RECORD OF MEDICINE

GENERAL PRACTICE CLINICS

VOL. 167 NO. 9 SEPTEMBER 1954

INTERNATIONAL RECORD OF MEDICINE

AGRANULOCYTOSIS ASSOCIATED WITH PHENYLBUTAZONE THERAPY *Otto R. Gsell*

GASTROINTESTINAL INFLUENCES ON SEIZURES IN THE INSTITUTIONALIZED EPILEPTIC *Madelin Perry*

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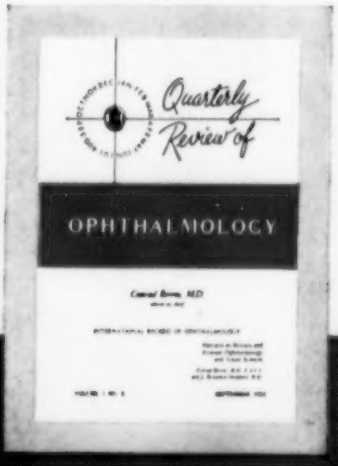

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2. Balfour, D. C., Jr.: in press.
3. Editorial: Internat. Rec. Med. 166:283, 1953.
4. Sternberg, S. D., and Greenblatt, I. J.: Ann. Allergy 9:190, 1951.
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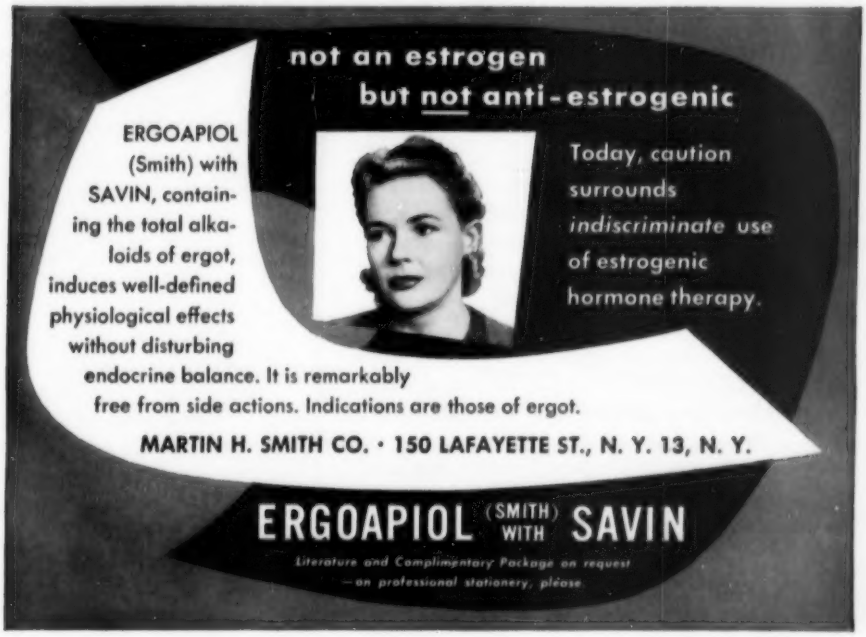
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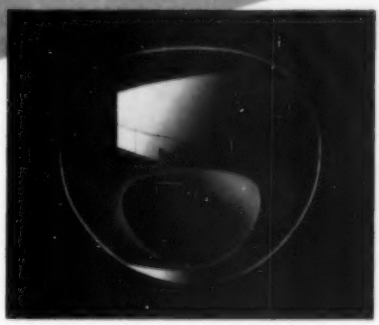

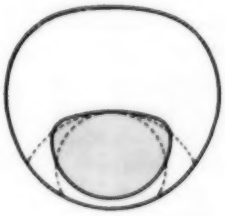

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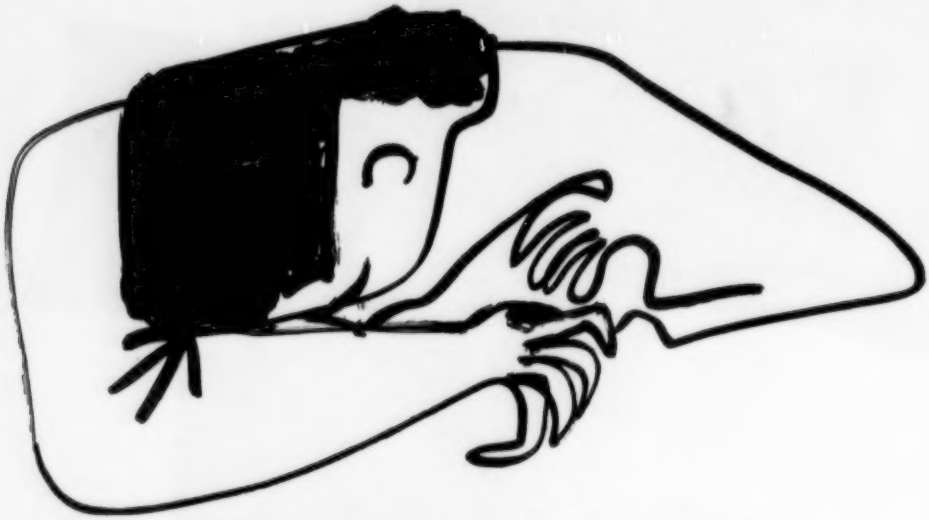

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1. Freed, S. C.: Internat. Rec. Med. 166:465 (Nov.) 1953. **2.** Rees, L.: J. Ment. Sc. 99:62 (Jan.) 1953. **3.** Morton, J. H., et al.: Am. J. Obst. & Gynec. 65:1182 (June) 1953. **4.** Morton, J. H.: Internat. Rec. Med. 166:505 (Nov.) 1953.

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RECORD OF MEDICINE

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Agranulocytosis Associated with Phenylbutazone* Therapy

Otto R. Gsell, M.D.†

SAINT GALL, SWITZERLAND

In the past two years during which phenylbutazone (Butazolidin) has been widely used with good results in central Europe, no injurious effect upon blood-forming tissues has been observed in this area. However, a number of cases of agranulocytosis directly related to phenylbutazone therapy has been observed in Anglo-Saxon countries. According to the publications of various authors, there can be no doubt that this drug, being a pyrazol derivative, can exert an injurious effect on the myeloid system. It now becomes desirable to determine the frequency of this occurrence and its relationship to the total number of doses administered, and to ascertain whether or not it may be possible by means of suitable precautionary measures to decrease the dangers associated with this extremely valuable medication.

As indicated in papers by von Rechenberg of the author's clinic, injury to blood-forming tissues of the body is much less frequent with phenylbutazone than is the case with dipyrin or aminopyrin. Three patients, who had shown agranulocytosis or severe neutropenia following dipyrin administration, manifested a prompt agranulocytic reaction following small doses of pyramidon in test experiments. On the contrary, no change occurred in the white blood picture following massive doses of phenylbutazone. This might possibly be due to the production in the organism of different metabolites in the biotransformation of phenylbutazone and of dipyrin.

In the 29 cases of agranulocytosis due to phenylbutazone, published in the world literature up to August, 1953, of which 5 should rather be regarded as severe cases of granulocytopenia with neutrophil values between 20 to 50 per cent (tables I and II), it is striking that these complications occurred early, that is, within two to eight weeks after therapy was begun, and that 26 of the 29 were associated with the oral and not with the injectable form of the drug. Agranulocytosis therefore did

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† Chief of the Medical Clinic, Kantonsspital, Saint Gall, Switzerland.

not occur in general in patients who received prolonged therapy at high dosage levels, but, with a single exception, it affected patients under treatment for between 7 to 60 days. The average dosage of phenylbutazone used was low, being between 400 and 600 mg. per day. Only 4 of the 29 patients received a daily dose of 1,200 mg. In isolated cases blood dyscrasia may follow a very short period of treatment with phenylbutazone, as indicated by the case of Jarvis, in which a daily dosage of 1,200 mg. had to be discontinued on the seventh day because of abdominal discomfort and nausea. Exanthema appeared on the following day, and at the end of one week clinical symptoms of agranulocytosis with soreness of the mouth and throat manifested themselves. In the case reported by Dilling, edema of the hands and legs appeared after five days during which time the daily dosage of the drug was 600 mg. After an interval of seven days therapy was resumed with a dosage of only 400 mg. per day. The patient manifested diarrhea and vomiting three days later and after five days presented the complete picture of agranulocytosis. One late case of agranulocytosis, which occurred during an intercurrent infection and which was followed by rapid recovery, was reported by Kuzell et al.[1] This 36 year old patient had been taking 400 to 600 mg. phenylbutazone daily for nine and one-half months, previous to which a combination of phenylbutazone and aminopyrine had been taken over a period of six months in a daily dosage of 750 to 1500 mg. Intramuscular injections were administered only in two cases by Kuzell and in one case by Procter, and in these only occasionally, as a concomitant of daily oral medication. Often the onset of agranulocytosis was preceded by an intercurrent infection and in many patients by nonspecific symptoms of allergy, such as fever, malaise, cutaneous eruptions (rash occurred in 8 out of 23 patients described), and agranulocytosis often being manifest only after continued use of the drug.

No predilection as to age seems to exist. Twenty of the 23 patients were between 43 and 73 years of age. Only three were young adults (24, 26, and 36 years old respectively). The female sex distinctly predominates inasmuch as 20 of these patients were females and three were males. However, it is to be borne in mind that chronic rheumatoid arthritis, one of the principal conditions for which phenylbutazone is indicated, occurs much more frequently in females than in males.

The pathogenesis of agranulocytosis is, according to the weight of evidence, of an allergic nature. This view is supported not only by the occurrence of simultaneous or preceding allergic symptoms such as rash, fever, and nausea, but also by examinations of the bone marrow and by the rapid spontaneous recovery of the circulating blood after discontinuation of the drug in cases which are diagnosed early. The sternal marrow was examined in 11 patients (cases 4 to 8, 13, 18, 19, 22 to 24), seven of which recovered completely. An arrest of maturation with a sharp decrease in myeloid elements was observed in all, but never a purely fatty marrow, or a marrow containing reticulum cells exclusively. This indicates bone marrow depression due to an allergic process. If the medication is discontinued promptly and the patient given antibiotics during the agranulocytic phase, complete recovery can usually be hoped for. Even in the case reported by Proctor, which terminated fatally due to pneumonia, there was already a good degree of regeneration observed in the bone marrow at autopsy. It is also worthy of note that Kuzell again prescribed phenyl-

TABLE I

Agranulocytosis Following Phenylbutazone (Butazolidin)

Case No.	Author	Journal	Age & Sex	Butazolidin: Daily Dose mg.	Butazolidin: Period of therapy	Agranulocytosis lowest values: Leucocytes	Agranulocytosis lowest values: Polyn. %	Result
1.	Crowther and Elgood	Lancet. *2*:829, 1952.	66 F.	1200 then 600	17 days	2,450	0	Cured
2.	Jarvis	Lancet. 2:830, 1952.	59 F.	1200	7 days	4,000	4	Cured
3.	Stifel and Burnheimer	J. A. M. A. *151*:555, 1953.	52 F.	600	38 days	750	0	Cured
4.	Werblow and Neber	J. A. M. A. *151*:1286, 1953.	65 F.	600	14 days	2,650	17	Cured
5.	Etess and Jacobson	J. A. M. A. *151*:639, 1953.	74 M.	600 then 400	approx. 50 days	700	9	Died (Pneumonia)
6.	Bershof and Oxman	J. A. M. A. *151*:557, 1953.	68 F.	600 then 400	approx. 40 days	3,100	0	Cured
7.	Hinz et al	J. A. M. A. *151*:38, 1953.	43 F.	400	46 days	1,500	6	Cured
8.	Steinberg et al	J. A. M. A. *152*:33, 1953.	52 F.	400	26 days	650	0	Died (Pneumonia)
9.	Kuzell et al	Arch. Int. Med.: in press, 1953.	67 F.	400	approx. 60 days	1,400	8	Cured
10.			57 M.	600	approx. 30 days	1,800	13	Cured
11.			49 F.	600	approx. 45 days	2,080	6	Cured
12.			36 F.	400–800	9½ months	2,020	1	Cured
13.	Kiely and Stickney	Proc. Staff Meet. Mayo Clin. *28*:341, 1953.	56 M.	600	50 days	600	0	Cured
14.	Breen and Emond	Brit. Med. J. *1*:991, 1953.	24 F.	400	10 days	1,800	50	Cured
15.	Newns	Brit. M. J. 992, 1953.	59 M.	400	approx. 60 days	?	0	Died (Pneumonia)
16.	Leonard	Brit. Med. J. *1*:1311, 1953.	53 M.	1600 then 800	approx. 40 days	1,600	34	Cured
17.	Nassim and Pilkington	Brit. Med. J. 1310, 1953.	?	?	?	1,700	39	Cured
18.	Dilling	Lancet. *1*:1230, 1953.	53 F.	600 then 400	9 days	1,400	0	Died (Multiple gastric ulcers)
19.	Kersley and Mandel	Lancet. *1*:1046, 1953.	46 F.	400 then 200	20 days	850	0	Cured
20.	Proctor and	Lancet. *1*:1047,	26 F.	1200	18 days	?	?	Cured
21.	Evans	1953.	43 F.	600	approx. 30 days	200	0	Died (Pneumonia)
22.	Brandwein	N. Y. State J. Med. 53:1577, 1953.	43 F.	600	21 days	2,000	5	Cured
23.	Kaplan	Bull. Dade County M. A. 23:43, 1953.	60 F.	?	20 days	2,650	20	Cured
24.	Loxton et al	Lancet. 2:682, 1952.	? F.	400	?	?	?	Cured
25.	"Medico legal"	Brit. M. J. 2:1427, 1952.	57 F.	?	(97 tablets)	?	?	Died
26.	Rice	Lancet. *1*:192, 1953.	44 F.	?	?	?	?	Died (Pneumonia)
27.	Englemann	Ann. Rheumat. Dis.	?	?	?	?	?	Cured
28.	Englemann	*12*:in press, 1953.	?	?	?	?	?	Died
29.	Hollander	Ann. Rheumat. Dis. *11*:300, 1952.	?	?	?	?	?	Cured

TABLE II

Side Effects—Phenylbutazone—(1952–53)

Side Effects Affecting		Authors	Smith Kuna	Stephens et al	Bach	Hindley Smith	Davies et al	Hart Johnson	Granirer	Loxton Le Vay	Smith	Kling	Hollander	Shulmann	Hughes	Slot	Usobiaga	Salvini Grandonico	Lucchesini Cecchi	Byron Orentstein	Belart	Nassim Pilkington	Freeland Storey et al	Kidd Boyce	Patterson et al	Cudkowicz Jacob	Huber Binswanger	Achardi et al	Barcello Serra	Currie Will Brown	Rowe et al	de Sego Leverenius	Rechenberg	Steinbrecker Berkowitz	Kelly	Gilhespy	Kuzell et al	Total No. of Individual Side Effects
Water balance	Edema, water retention			9			8	3	6	3				2	3				3	5	4	1	6	7		8				4	11	8	5			2	100	198
Gastro-intestinal tract	Nausea, vomiting, intestinal disturbances	2	2	2		25	2										1	4	4		21	35	25		6				6	4	14				16	106	275
	Activation of ulcers		7					1		1													3	1	2					1						3	19
	Hematemesis Melena		2				3	1										1				1			2										3	13
	Jaundice																												1							2	3
Blood	Anemia		18		2			2												2																14	38
	Leukopenia							1																22												17	20
	Agranulocytosis								1			1									1															4	7
	Reduction of plateleta		31													2																			1	34
	Hematuria		2																						5						14					21
Skin	Exanthema, pruritus, purpura	2	9			4	6	4	5	1			1					1	4		6	15	8					4			1			5	44	120
	Stomatitis																												1						2	21	24
Central Nervous System	Drug fever						1																													1	2
	Vertigo																			1		3														30	34
	Euphoria		3																					2													5
	Nervousness, malaise																					6									5				17	28
	Other side effects				17																									6			22	35	2		82
	Total number of cases treated	30	188	50	140	100	60	20	50	19	109	47	239	20	4	35	47	28	131	200	109	164	104	32	50	52	20	125	424	174	550	125	200	200	50	800	

butazone in three of his four cases after recovery and observed absolutely no effect on the granulocytes. It therefore may be surmised that the condition represents an isolated, transitory allergic reaction that may have been conditioned by a secondary infection.

Of the 8 fatal cases, 5 were caused by pneumonia supervening upon agranulocytosis and 1 by gastrointestinal bleeding in a patient who had a stomach ulcer (Dilling). Detailed information is lacking concerning the 2 remaining deaths. The case of Steinberg appears to be somewhat different in that the patient had received 20 units of ACTH daily from June 13 to July 22. Previous to this the patient had been given 75 mg. of cortisone daily for nine months. Four hundred mg. of phenylbutazone was administered daily from August 5 to September 2, while ACTH was continued every other day. The patient manifested nausea and a rash on September 2. On September 9, the full picture of agranulocytosis was manifested with a leucocyte count of 600, and on September 12 the patient died of pneumonia in spite of 25 units of ACTH, given to the patient every six hours starting September 9, as well as five blood transfusions. Since severe degenerative changes of the adrenal cortex were found at autopsy, the rapidly fatal course and lack of healing tendency may be considered as due to corticotropic therapy. The pathologic diagnosis of the bone marrow was "hyperplasia with maturation arrest of the bone marrow."

If we consider the incidence of agranulocytosis associated with phenylbutazone therapy, the number of cases are small in proportion to the total number of cases treated. Undesirable side effects of this nature are usually published at once when a new product is under investigation. According to the British journal *Lancet*, approximately 100,000 patients received phenylbutazone up to the autumn of 1952. Only 14 cases of agranulocytosis had been reported from all of Great Britain approximately one year later. Currie, Brown, and Will observed no such toxic effect among 848 cases treated in Glasgow. De Seze in France reported an incidence of toxic effects in 1.8 per cent with no instance of injurious effect upon the blood observed among the patients studied. Reports from Switzerland likewise have included no cases of agranulocytosis. In the clinic at Saint Gallen, where phenylbutazone was administered to almost 1,000 patients up to August 1, 1953, in various forms including ampuls, tablets, and suppositories, not a single case of agranulocytosis has been observed nor has any serious damage to erythropoiesis or thrombocytopoiesis been encountered. Data gathered from publications providing statistics up to July, 1953, indicate that out of 4,696 cases treated, agranulocytosis occurred in only 7 or 1.5 per cent of the total number of patients (table II). With the exception of the Engleman case (on which details are lacking), all of these patients, which were under close clinical supervision, recovered fully, whereas the 22 cases reported assertively in various publications mainly derived from patients who had not been so closely watched. The actual incidence of agranulocytosis should be considerably less than 1.5 per cent if the figures from England and Central Europe are used for comparison.

Because of the infrequency of occurrence of agranulocytosis during phenylbutazone therapy and the favorable prognosis for recovery both in the early allergic stages as well as from the very rare and perhaps toxic late effects, there is not sufficient reason to abandon this drug since the outstanding merit of the product warrants the risk

of infrequent undesirable side effects. Nevertheless, it is absolutely essential that every precaution be taken to avoid as far as possible any untoward effect upon the blood.

Regular examinations of the blood are recommended as a precautionary measure in phenylbutazone therapy. A complete examination of the blood should be made before treatment is begun. The leucocyte values should be checked weekly for the first two months and semimonthly or monthly counts should be done thereafter. High dosages are recommended only for short periods of time, the generally recommended dosage being 400 to 600 mg. daily by mouth.* The medication should be discontinued immediately if symptoms of intolerance are observed such as nausea, rash, stomatitis, or petechiae, or if the leucocyte count goes below 3,000 with a decline in neutrophils to below 50 per cent. In such cases a thorough study is required before therapy is resumed. An oral test dose of 200 to 400 mg. should be given and leucocyte counts should be made after two, four, six, and ten hours, as advocated by von Rechenberg. Furthermore, the question of other medicaments which might contain aminopyrin should not be overlooked.

With an understanding of the side effects of phenylbutazone and by observation of the aforementioned precautions, this drug, in the author's opinion, may be administered without hesitation. This product is a valuable contribution to the therapy of inflammatory and rheumatoid conditions, and with the cortisone preparations it represents a most important advance in the therapy of the rheumatoid diseases.

SUMMARY

The cases of agranulocytosis which have been observed during phenylbutazone therapy and reported in the literature to date have been reviewed, and the relatively rare occurrence of this complication in relation to the extensive use of the drug has been discussed. With proper precautions there should be no hesitation in taking advantage of the therapeutic properties of phenylbutazone.

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* Seven times or twice weekly dose of ½ to 1 ampul parenterally, that is 500 to 1000 mg.

Gastrointestinal Influences on Seizures in the Institutionalized Epileptic

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The over-all management of epilepsy both in and out of institutions almost always includes advice to establish regular bowel habits. Under the heading of hygienic measures, the patient is told to get plenty of fresh air, exercise, eat a regular diet with an abundance of vegetables, and move his bowels regularly. The importance of such measures was recognized even in early historical times: Diocles[1] recommended purgatives, diuretics, walking, and exercise. Serapion[2] prescribed a regular regimen of diet and exercise along with cathartics one or two days preceding an attack—providing the attacks followed a definite rhythm. Asclepiades[3] among other things recommended enemas and suppositories. Galen's[4] chief emphasis was on exercise, a wholesome diet, purgatives, and bleeding. Celsus[5] a contemporary of Galen stated that all provoking factors like heat, cold, drunkenness, etc., must be avoided. For acute attacks "All patients, however, should be purged by enemas or black hellebore." John of Gaddesden[6] divided the treatment of epilepsy into six parts. The first part concerned "empirics," the second, diet, exercise and climate; the third, emetics; the fourth, purgatives, suppositories and phlebotomy; the fifth, sternutatories and rubefacients; and the sixth, causes or sites of origin. Merritt[7] has summarized the modern views by stating: "Bowels can be regulated by training, and, if necessary, by the judicious use of mild laxatives." Aird[8] states, "The second main aspect of anticonvulsive therapy is concerned with the regulation of all factors influencing convulsive susceptibility. Under this heading may be included . . . the ruling out such possible contributing mechanisms as foci of infection, alcohol, allergies, . . . constipation, over-fatigue and emotional tensions. . . ."

Although this insistence on regular laxation has been maintained from ancient times until the very present, little is known in a quantitative way of the patterns of laxation in the epileptic. This report concerns some studies on the relation between laxation and epilepsy, and some incidental correlations between weight changes and seizures.

METHODS

The subjects represented a random sample of ambulatory female epileptic patients in a state institution, who were selected solely on the basis that they were all in one residential unit, that they had a reasonably good memory and were generally cooperative. This unit was fully representative of the 8 other units in this institution of a similar size as regards the type of patient, severity of the epilepsy, and defecatory patterns.

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TABLE I

Bowel Movements by Type of Seizure

Type of Seizure	Number of Subjects	Average Number of Bowel Movements per Week		
		Pretreatment Control Period	Treatment Period	Post-treatment Control Period
Grand mal and Petit mal*	10	5.00	11.00	4.90
Grand mal only	9	5.42	15.22	7.64
Petit mal only	3	6.00	15.59	4.34
No seizures	12	6.31	13.85	7.35
Total	34			
Average		5.66	13.53	6.44

* Significantly different from the other types (P = 0.05).

The study was started with 55 subjects, 13 of whom dropped out or were discarded for noncontributory reasons (intercurrent illness, transfer, inability to give reliable answers, etc.) before the observations were completed. The laxative medication was given along with their regular antiepileptic therapy after meals. All of the patients were accustomed to taking medication daily and having it occasionally varied, so that the addition of laxative tablets was not accompanied by any emotional reaction, and they were not told that the additional tablets were laxatives. Throughout the study they were allowed laxatives and enemas at their own request in the same fashion as nonstudy patients.

The subjects were interviewed and weighed once a week. The following information was elicited in the interview: the number and type of seizures, the number of bowel movements and the character of the feces (hard, medium, loose, watery), the presence of straining or griping with defecation, whether or not cathartics or enemas were taken, the presence of gas, indigestion, or belching, along with an expression of their opinion as to their general state of well-being and appetite.

The subjects were studied for a control period of four weeks, then given a commonly used laxative (caroid and bile salts with phenolphthalein*) 4 tablets daily (2 each morning and evening) for the next four weeks while the observations were continued. After this there was a post-treatment control period of four weeks.

RESULTS

Of the 42 subjects who completed the full 12 weeks of observations, 8 were unable to take the full dose of laxative and were given one-half the dose morning and

* Caroid and bile salts with phenolphthalein: Per tablet—bile salts compound, 1⅛ grain; ext. cascara sagrada, ¾ grain; phenolphthalein, ½ grain; ext. nux vomica, 1/16 grain; capsicum, 1/10 grain; and caroid® (papain), 1¼ grain.

evening. The data for these 8 has been tabulated and analyzed separately and by and large the results were identical with those obtained in the group of 34 patients.

Bowel Movements: Table I presents the correlation between the average number of bowel movements per week and the type of seizures which the patient had during the course of the study. Table II, which presents this same data arranged by weeks of medication rather than by seizure type, enables one to gain some concept of the variability of the data.

The mean values for the three periods of the study (pretreatment control period, treatment period, and post-treatment control period) were 5.66, 13.53 and 6.44 bowel movements per week for the 34 patients taking 4 tablets a day during the treatment period. For the 8 patients taking 2 tablets a day, the corresponding values were 6.38, 14.17 and 7.75. The mean values for the 34 patients are all statistically significant from one another at a probability level of 1/100 ($P = 0.01$). The addition of the 8 patients taking 2 tablets a day to the 34 does not alter the statistical significance of the differences between the means. It is especially noteworthy that the increase in the number of movements in the post-treatment control period over the pretreatment control period is not due to a large number of movements in the first week or so but is apparently a sustained increase indicating improved function.

The change in consistency of the feces (table III) also reflects a laxative effect. It would appear that the change in consistency of the stools produced by the laxative did not persist after the medication was discontinued, in contrast to the effect observed with number of movements. However, it is important to note that total bowel function was better in the post-treatment period than in the pretreatment one.

TABLE II

Bowel Movements by Week of Observation

Week of Observation	Number of Subjects	Pretreatment Control Period	Treatment Period	Post-treatment Control Period
First	34	5.38	13.91	6.18
Second	34	5.85	12.68	6.53
Third	34	5.88	13.41	6.18
Fourth	34	5.53	14.12	6.88
Average		5.66 ± 0.12	13.53 ± 0.32	6.44 ± 0.17

TABLE III

Consistency of Stools Calculated as Per Cent

Stool Consistency	Pretreatment Control Period	Treatment Period	Post-treatment Control Period
Watery	0	0	0
Loose	4	52	8
Medium	70	38	65
Hard	26	10	27

Cathartics and Enemas: The subjects were given cathartics and enemas at their own request in addition to the laxative which they took regularly during the middle period of the study. This was to avoid any undue attention in the change of laxative component in their regimen and also to gain insight to their spontaneous needs during the medication period. This use of cathartics and enemas is tabulated in tables IV and V. Table IV shows that the use of the stronger laxatives was very nearly discontinued during the caroid and bile salts medication period, but that mineral oil continued to be used in substantial though decreased amounts. Mineral oil has been omitted in constructing table V since its action is of an entirely different type than that of the cathartics and enemas.

Seizures: The number and types of seizures which occurred in the group of 34 patients taking the full dose of laxative are tabulated in tables VI and VII. The table shows that there was only a small decrease in the number of grand mal and petit mal seizures while taking the laxative. However, 1 patient had seven grand mal seizures during the pretreatment control period, one seizure while getting the

TABLE IV

Elective Use of Cathartics, Enemas and Mineral Oil
(by medication)

	Total Number of Times Used by 34 Subjects		
	Pretreatment Control Period	Treatment Period	Post-treatment Control Period
Cathartics			
Cascara Sagrada	76	17	87
Milk of Magnesia	16	2	11
Compound Cathartic	18	2	22
Epsom Salts	21	4	22
Castor Oil	1	0	0
Total	132	25	142
Enemas	8	7	12
Mineral Oil, plain and emulsion	121	89	145

TABLE V

Elective Use of Cathartics and Enemas
(by patient weeks)

	Pretreatment Control Period	Treatment Period	Post-treatment Control Period
Number of Weeks in which a cathartic was requested.	74	19	73
Number of Weeks in which no cathartic was requested.	62	117	63

TABLE VI

Influence of Treatment on Number of Grand Mal Seizures per Week in 34 Patients

Weeks of Period	Pretreatment Control Period	Treatment Period	Post-treatment Control Period
First	9	10	12
Second	17	12	14
Third	11	14	15
Fourth	12	10	10
Average	12.2	11.5	12.8

TABLE VII

Influence of Treatment on Number of Petit Mal Seizures per Week in 34 Patients

Weeks of Period	Pretreatment Control Period	Treatment Period	Post-treatment Control Period
First	7	6	10
Second	12	7	13
Third	11	2	2
Fourth	5	11	6
Average	8.75	6.5	7.75

laxative and eleven during the post-treatment control period. This patient was put back on the laxative and had no seizures for a month. On being taken off the laxative medication for a third control period, she again had seizures. On the other hand, another patient had three seizures during the control period, eleven seizures during the treatment period and four seizures during the post-treatment control period. During the treatment period, this same patient became emotionally perturbed in regard to problems unrelated to the laxative study. If this particular patient were dropped from the tabulation, there would be a statistically significant decrease in seizures for the period when the caroid and bile salts were given. In considering possible explanations as to why one patient was benefited so much by the use of the laxative, the idea was contemplated that it might be due to dehydration. However, the average weight was 135¼, 135¾, 136½ pounds respectively during the first three study periods, which makes it appear unlikely that any dehydration occurred at the time that this patient had a reduced number of seizures.

In addition to considering the correlation between weight changes and seizures for the one patient, who was markedly benefited by taking the laxative, the correlation was determined for the group as a whole. The relation between weight gain or weight loss and grand mal seizures is tabulated in table VIII. For all 34 patients in the study, the number of weeks in each category was as follows: weeks with weight gain, 139; weeks with no change in weight, 144; weeks with weight loss, 125; which indicates that the group of 19 having grand mal seizures was about the same as the group as a whole as regards the number of weeks in each category.

Instead of tabulating the number of weeks in which seizures occurred, one could consider the actual number of seizures. Nineteen patients had grand mal seizures during the study. In the 73 weeks where there was a weight gain, there were 45 grand mal seizures. In the 74 weeks where there were no weight changes, there were 33 seizures; in 75 weeks where there was a weight loss, there were 117 seizures. This further substantiates the data obtained in a tabulation by weeks. This difference in number of seizures between weeks with weight gain and weeks with weight loss is statistically significant according to a Chi square test with $P<0.05$.

The actual weight changes during weeks when there was a weight gain averaged 1.68 pounds per patient, and during weeks of weight loss, 4.36 pounds. There did not appear to be any correlation between weight changes and the occurrence of petit mal seizures.

Weight: The data on weight changes have largely been presented in connection with seizure data. However, for the group of 34 as a whole (table IX) a weight gain was shown by 24 of the 34 patients. It would seem to indicate an improvement in the nutritive state of the patient.

Symptoms: Table X reports the frequency of straining and griping at defecation, indigestion, gas (flatus), and belching.

Subjective Feeling: The patients were asked how they felt and about their appetites; the results are presented in table XI. The subjects felt better while taking the caroid

TABLE VIII

Weight Changes and Grand Mal Seizures

(Analysis of data on 19 subjects who had a grand mal seizure at some time during the study)

	Weight Gain	No Weight Change	Weight Loss
Weeks in which one or more grand mal seizures occurred	16	18	33
Weeks in which no grand mal seizures occurred	57	56	42
Total number of weeks	73	74	75

TABLE IX

Weight Changes per Period

Period	Total Wt. Change for All 34 Patients lbs.	Average Wt. Change per Patient lbs.	Number Losing Weight	Average Weight Loss lbs.	Number Gaining Weight	Average Weight Gain lbs.
Pretreatment Control	−29	−0.85	17	2.9	10	2.0
Treatment	+50	+1.47	6	2.3	24	2.7
Post-treatment Control	−9	−0.26	14	2.1	10	2.1

TABLE X

Total Number of Weeks in Which a Patient Reported Symptoms

Symptoms	Pretreatment Control Period	Treatment Period	Post-treatment Control Period
Straining*	52	11*	55
Griping	18	26	28
Indigestion	12	13	18
Flatus	63	54	60
Belching	66	54	54
Total	211	158	215

* Statistically significant (P = 0.001).

and bile salts with phenolphthalein tablets. The difference between the number feeling good during the pretreatment control and during medication period was highly significant statistically (P = 0.001).

DISCUSSION

Laxative Effects: From examination of table I it would appear that the patients suffering from the most severe epilepsy, i.e., those having both grand mal and petit mal seizures were the most constipated. Those with either type alone were less constipated, and those with no seizures at all during the period of the study were the least constipated. This does not necessarily mean that constipation is a cause of epilepsy, but it could mean that the occurrence of frequent seizures may lead to or be associated with constipation. In view of the fact that cerebral centers may influence the gastrointestinal tract,[9] that epilepsy may manifest itself only or primarily by gastrointestinal symptoms,[10] and that patients with psychoses are generally constipated,[11] this association of constipation and severe epilepsy would seem to be quite reasonable.

TABLE XI

Distribution of Subjective Responses

Subjective Phenomena	Status	Pretreatment Control Period	Treatment Period	Post-treatment Control Period
Sense of Well-Being	Good	6%	25%*	20%
	Fair	89%	69%	66%
	Poor	5%	6%	14%*
Appetite	Good	7%	15%*	9%
	Fair	89%	81%	82%
	Poor	4%	4%	9%

* Statistically significant (P = 0.05 or less).

During the post-treatment control period there was a significant increase in the number of bowel movements over the pretreatment control period, even though the stool consistency during this period was the same as in the pretreatment period, according to table II. This data is in direct contradiction to the commonly accepted teaching that if laxatives are given continuously for any period of time they result in dependence or habituation and may even cause constipation. At least if this statement is true for some laxatives, it certainly does not seem to apply to the one used in this study. As a matter of fact, it would seem that the caroid and bile salts with phenolphthalein tablets, when given daily for a month, produces a prolonged improvement in bowel function which outlasted the treatment period. This does not appear to be due to increased use of laxatives or cathartics during the post-treatment control period inasmuch as the uses during the pretreatment and post-treatment periods were substantially the same (table IV).

Seizures: There seems little reason to doubt that the number of grand mal seizures experienced by some of the patients was decreased by the caroid and bile salts with phenolphthalein therapy. It has long been recognized that epilepsy is an exceedingly variable disease and that innumerable technics will precipitate or prevent attacks. From ancient to modern times the therapy of epilepsy is replete with nostrums and technics now discarded that worked in a few cases, ketogenic diet[12, 13, 14] and dehydration,[15, 16] being among the more recent ones. Among the measures consistently recognized as having some effect on epilepsy is laxation either by cathartics or enemas. The data reported in this paper are consistent with this historical experience in that an occasional patient is greatly benefited by the judicious use of a laxative. In this regard it is interesting to note that Wolf[17] reported magnesium sulfate in doses of 0.6 to 17.0 Gm. was effective in controlling seizures in some patients. He was, however, primarily interested in blood magnesium levels and made no observations about laxative effects.

Speculations about the mechanisms whereby laxatives affect grand mal seizures would seem to be unwarranted here. It is well known that psychologic factors influence the frequency of grand mal seizures. Any particular therapy that is effective may be so because of psychologic factors or because of some alterations in the basic physiology of the body (neural reflexes, altered water balance, release of circulating hormones, etc.). In studying the effect of ketogenic diet, dehydration, or laxatives, it would appear impossible or at least exceedingly difficult to dissociate any physiologic effect from a psychologic one. All one can say is that under certain conditions a particular patient appears benefited by a particular regimen, and perhaps it might be useful to other patients.

In passing it should be noted that there was no weight loss and, hence, no dehydration while the subjects in this study were taking laxatives. Therefore, any effect on seizures could not be due to dehydration.

Of particular interest is the correlation between weight changes and the occurrence of grand mal seizures. Apparently, grand mal seizures are more apt to occur, and to occur more frequently, at a time when the patient is losing weight. Petit mal seizures do not seem to be influenced by weight changes. What this means in terms

of overall metabolic changes, etc., is not clear. It may be that a loss of weight tends to cause seizures or that an increase in the number of seizures tends to cause a loss of weight. The former would appear to be the more likely explanation, and if true it seems that the oft-repeated advice that an epileptic should lead a smooth and even existence is well warranted. Any deviation from such an existence, such as excessive exercise, minor illnesses, etc., that might result in weight loss, would tend to lead to an increase in the number of seizures.

Weight and Appetite: The subjects gained an average of 1½ pounds each during the four weeks when they were taking tablets of caroid and bile salts with phenolphthalein in contrast to losses during the control periods (table IX). This gain in weight is undoubtedly due to increased food intake as a result of an increase in appetite during this same interval (table XI). The weight gain could be due to water retention, but there does not seem to be any good reason why the subjects should be retaining water in the presence of increased laxation.

The increase in appetite which probably caused the weight gain, might in turn be due to either an increase in well being associated with increased frequency of defecation or due to the digestive capacity of the papain contained in the caroid product. A choice between the two alternatives cannot be made on the basis of this study. However, by enhancing the digestion of protein with caroid, the frequency and amount of indigestion might well be decreased due to a decrease in the amount of allergenic partially digested protein.

Symptoms: The only defecatory symptom that was significantly different during control and treatment periods was straining. A decrease in straining at defecation would appear to be perfectly logical in view of the softer consistency of the stools. It is interesting that this decrease in straining was not accompanied by a significant increase in griping. Of equal interest is the fact that flatus did not decrease as one might have expected. The mechanism of production and factors influencing flatus production have never been adequately examined. It would seem that the facile explanation that increased flatus production is due to the feces remaining too long in the gastrointestinal tract is inadequate.

Sense of Well-Being: The group of patients studied very definitely felt better while they were taking caroid and bile salts with phenolphthalein. It might have been due to psychologic factors connected with increased defecation. Equally likely, however, is the possibility that the subjects felt better because of less absorption of indole or other products from the large bowel. On the other hand, well-being may have been associated with a better appetite. This increased sense of well-being continued after the medication was stopped. An explanation of the persistence of the sense of well-being is not apparent at this time.

SUMMARY

1. In this study the patients having both grand mal and petit mal seizures at fairly frequent intervals tended to be more constipated than patients with only occasional seizures or seizures of either type alone.

2. Weight loss seems to be associated with an increased frequency of grand mal seizures.

3. One patient had a very definite decrease in seizures while on laxative therapy, and the group as a whole tended to have about 10 per cent fewer seizures during such treatment.

4. The laxative used in this study, tablets of caroid® and bile salts with phenolphthalein, when given daily for a month, produced no evidence of habituation or tolerance, but on the contrary seemed to produce a prolonged improvement in bowel function which was accompanied by gain in weight and an increased sense of well-being.

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MEDICAL HUMANITIES

Osler

Part 1: Student, Professor, Author*

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The life of Sir William Osler cannot be told too often. Several years ago, when I knew little about medicine and almost nothing about Osler, I chanced upon Cushing's account of the great Canadian doctor: a Pulitzer Prize winner and one of the best biographies ever written. I was so impressed by the book that I went on to read Osler and do a master's thesis on Sir William as a literary man. Many others were similarly moved by Cushing. In the May, 1953, *Reader's Digest*, to cite a recent example, Richard Match's "The World's Best Doctor" says: "Anyone who undertakes to tell the story of Osler must acknowledge his debt to Dr. Harvey Cushing's 1,400 page authorized *Life of Sir William Osler*, published in 1926." Professor Gilbert Highet's radio talk, "Science and Humanism: Sir William Osler" (reprinted by the Oxford University Press in *People, Places, and Books* in 1953), concludes: "This is chiefly what people love about Osler: his ability to show the world that science is not a dehumanized activity carried out by calculating machines, but the work of live men devoted to the cause of better life; his strong sense that research is part of the general and broader activity of learning, teaching, and public information; his belief that science is only one part of the life of a scholar, however great a discoverer he may be, and that the appreciation of literature and, even more genuinely, the enjoyment of life, humor, and friendship are the better part, without which the investigator is a monk walling himself into his own cell and closing the windows." So here, once more, Osler's life story, with little added to Cushing, is told again.

I

Throughout the summer of 1897, Frederick Taylor Gates sat reading a heavy book. Mr. Gates was profoundly interested in what he read; there was, he said, a "fascination about the style itself" that led him on until he had finished all of the thousand or so pages, and an idea was born. For Mr. Gates, who was a member of John D. Rockefeller's philanthropic staff, had been charged with investigating projects through which Rockefeller's money might benefit humanity. The book

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was William Osler's *Principles and Practice of Medicine*. Out of the meeting of the man and the book grew the Rockefeller Institute for Medical Research.

Doctor Osler's textbook had given Gates a new notion of medicine. It did not prescribe drugs with abandon for the cure of every symptom and every disease, as did other medical textbooks of the day. It was instead a careful description of disease in the human body, together with what was known about improving the condition of the sick. Doctor Osler distinguished carefully between demonstrable truth, which he stated flatly as plain fact, and the conclusions of expert observers, which he stated as the best opinion available. There was remarkably little demonstrable truth in methods of treating disease, though there was a great amount of opinion, expert and otherwise. Gates was appalled at the realization—very few people, even among doctors, understood this at the time—that there were only two actual cures known to medicine, only two drugs which attacked and destroyed specific disease organisms in the body. Osler's textbook had performed the service to medicine of wiping clean a slate cluttered with misconceptions, and of showing clearly where the field of advancement for the profession lay.

The remarkable man who had written this book was, at the time, professor of medicine at the new Johns Hopkins University Medical School. Although a Canadian by birth and a British subject, he had spent most of his teaching years in the United States and exercised even at that time as much influence as any man upon the development of medical education and, therefore, of the practice of medicine in this country. Before Osler's day, the life of the medical student was taken up with listening to formal lectures and preparing dissertations out of books about disease he had never seen. He left school armed only with booklearning and a diploma, to wrench from his helpless patients the practical knowledge his education had neglected to give him. Osler took his students into the wards and the autopsy rooms, where they saw at first hand the diseases they had read about, and he wrote articles and editorials demanding this reform in all the schools. Today this method of bedside teaching is used in every medical school in the United States.

The zeal with which he carried on his work was part of an irrepressible, humorous, friendly, and widely loved personality. As child and young man, he was a mischievous imp of a fellow, much given to practical jokes, who had the great fortune to have parents who did not take his pranks seriously, were not given to corporal punishment, and who were so forgiving and affectionate that he undoubtedly got by with a good deal more than most boys. He lived to become Sir William Osler, baronet, Regius Professor of Medicine at Oxford University, probably the greatest living physician of his day, a man who tremendously influenced the teaching of medicine, and whose writing, teaching, and speaking were to determine the course of local, national, and even international, problems of public health, sanitation, and the effective control of disease.

William Osler was born July 12, 1849, in the Bond Head parsonage of Canon Featherstone Lake Osler. It was a happy childhood: genuine, natural, out-of-doors, wholesome. The boy, referred to by his father as "Little burnt-holes-in-a-blanket," because of his papoose-like complexion and black eyes, grew up, meeting

Bettman Archive

William Osler in his study in 1891 writing his world-renowned text book, *Principles and Practice of Medicine.*

a bear in a raspberry patch, enjoying the open air without benefit of organized sports, and soon studying in Bond Head with a Mr. Marling. But feeling that his children needed better educational facilities, Canon Osler asked Bishop Strachan of Toronto to transfer him to Dundas, where a rectorship was vacant and where life was less primitive and arduous. So in 1857 to Dundas the family moved, and here amid great natural beauty was found a comfortable parsonage, good schools, and congenial, cultivated friends.

In the fall of 1864, the boy was sent to a boarding school in Barrie on the shores of Lake Simcoe, halfway between the Great Lakes of Huron and Ontario. Despite Osler's own statement, "In my school days I was much more bent upon mischief than upon books," he was easily the first boy in the school and was notably proficient in the Bible. At times, a zeal for study would overtake him, and a school friend, Ned Milburn, says that at 9:30 at night, when their lamps were taken away from them, they would study Xenophon, Virgil, or Caesar by the light of the full moon after jumping from their dormitory window; then go to the Bay a hundred yards away for a cool swim. In addition, he won at one time a school prize for kicking the football and excelled in other sports. Here, too, he showed that genius for friendship that never left him throughout his life, as attested by his hundreds of friends all over the world, with all of whom, it seems, he kept up a correspondence.

But, as the reputation of the Barrie school was falling, Osler's parents decided to send him to a new school at Weston, a few miles west of Toronto. Here it was, in

1866, that William Osler came under the first great influence of his life: the remarkable "Father" (the Reverend William Arthur) Johnson, founder and warden of Trinity College School. A naturelover, an artist, a wood-carver, a high-churchman, a scientist who believed that nature is beautiful even under the microscope, and a non-believer in the educational theory that facts must be drilled into students: Johnson was all this and more. As Osler told the story many years later:

> As a boy I had the common experience of fifty years ago—teachers whose sole object was to spoonfeed classes, not with classics but with syntax and prosody, forcing our empty wits, as Milton says, to compose "Theams, Verses and Orations," wrung from poor striplings like blood from the nose, with the result that we loathed Xenophon and his ten thousand, Homer was an abomination, while Livy and Cicero were names and tasks. Ten years with really able Trinity College, Dublin, and Oxford teachers left me with no more real knowledge of Greek and Latin than of Chinese, and without the free use of languages as keys to great literatures. Imagine the delight of a boy of an inquisitive nature to meet a man who cared nothing about words, but who knew all about things—who delighted in the woods in springtime, and who told us about the frog-spawn and the caddis-worms, and who read us in the evenings Gilbert White and Kingsley's *Glaucus*, who showed us with the microscope the marvels in a drop of dirty pond water, and who on Saturday excursions up the river could talk of the Trilobites and the Orthoceratites and explain the formation of the earth's crust. No more dry husks for me after such a diet.

So Willie was introduced by this remarkable man to the microscope, an instrument then much less familiar to students than it is today. Assuredly by his investigations into the mysteries of nature, into which he was led so delightfully by Johnson, the boy was forming the taste for natural science and the eagerness to know the truth which would lead to advanced scientific studies. Though he was not conscious of it, the two led him by sure instincts into the study and the practice and the teaching of medicine, where his human sympathies and his curiosity about nature could both have free play.

While he was still under the tutelage of Johnson, there came into Osler's life another character who was to develop and bring to full flower the tendencies which Johnson had aroused in him. This man, Dr. James Bovell, was to leave upon young Osler an impression probably more profound than that of any other man he would ever meet.

Bovell was medical director of Trinity College School at Weston. He practiced medicine in Toronto and taught in the Medical College; but on weekends he was in Weston with Johnson, searching the woods and streams for specimens and mounting them for their microscopical collection. The priest-naturalist and the doctor-naturalist (he too was to become a priest later) gave to the eager boy something of their curiosity about the things of nature, their gentleness of heart, and their "mystical and spiritual obsessions, but not their fanaticism." And whereas Johnson amazingly enough transmitted to a boy sixteen years of age an appreciation for Sir Thomas Browne's *Religio Medici* (which came to have a deep influence on Osler's way of life), it was Bovell whose name again and again Osler used to scribble in abstracted moments in later life on the margins of programs or lecture notes or any handy paper: "James Bovell M.R.C.P." or "James Bovell M.D."

As evidence of his growing personal and intellectual development, Osler was chosen head prefect of his school, and won the Chancellor's Prize as head of his

class at the end of the spring term in 1866. Though he had passed enough subjects to be admitted to college, Father Johnson urged him to remain at Weston for another year. The advice was heeded. That vacation, much time was taken up with Johnson and their search for specimens of natural life in the nearby forests and waterways. When he returned to school in the fall, he worked hard for a scholarship. In the autumn of 1867, he gained the Dixon Prize Scholarship, and went to Trinity College, Toronto, apparently with the study of theology in his mind. In the spring term he was still undecided about his future profession, but he was attending the Medical School in the afternoons, reading Lyell's *Principles of Geology* and preparing microscope slides at Dr. Bovell's, and it was not hard to see the direction of his inclinations. A few days after returning to Trinity in the fall for his second year in Arts, he announced to his parents and to the Provost that he was determined to go into medicine. When Dr. Bovell learned of this, he said to Osler, "That's splendid, come along with me," and for two years they lived much more like father and son than teacher and pupil. Fifty years later, Osler wrote:

> It has been remarked that for a young man the privilege of browsing in a large and varied library is the best introduction to a general education. My opportunity came in the winter of '69–'70. Having sent his family to the West Indies, Dr. Bovell took consulting rooms in Spadina Avenue not far away from his daughter Mrs. Barwick, with whom he lived. He gave me a bedroom in the house, and my duties were to help to keep appointments—an impossible job!—and to cut sections and prepare specimens. Having catholic and extravagant tastes, he had filled the rooms with a choice and varied collection of books. After a review of the work of the day came the long evening for browsing, and that winter gave me a good firsthand acquaintance with the original works of many of the great masters. After fifty years the position in those rooms of special books is fixed in my mind. Morton's *Crania Americana*, Annesley's *Diseases of India*, with the fine plates, the three volumes of Bright, the big folios of Dana, the monographs of Agassiz. Dr. Bovell had a passion for the great physician-naturalists, and it was difficult for him to give a lecture without a reference to John Hunter. The diet was too rich and too varied, and contributed possibly to the development of my somewhat "splintery" and illogical mind; but the experience was valuable and aroused an enduring interest in books. . . . Three years of association with Dr. Bovell were most helpful. Books and the Man!—the best the human mind has afforded was on his shelves, and in him all that one could desire in a teacher—a clear head and a loving heart. Infected with the Aesculapian spirit he made me realize the truth of those memorable words in the Hippocratic oath, "I will honour as my father the man who teaches me the Art."

At Toronto began what Osler called his "inkpot career": his first publication, a description of an episode of the holiday vacation of 1869, called "Christmas and the Microscope," was printed in a semipopular London journal on nature study called *Hardwicke's Science-Gossip* (now extinct) on February 1, 1869. Before his life was finished, he would have written hundreds of articles and books that would change the whole aspect of the education of the medical student in North America. Some of these were of interest only to the profession; but many others, such as *Aequanimitas* and *The Student Life* are so broad, so human, and so genuinely understanding and sympathetic that they have given inspiration and guidance to young men and women —and old ones, too—of many divergent interests. Concerning these writings, there will be more to say later.

Because of its better clinical facilities, Dr. Bovell thought it best that his pupil transfer from Toronto to McGill University in Montreal. Before leaving for the West Indies that summer (1870), Bovell must have given Osler a letter to Palmer

Howard, then Professor of Medicine at McGill. Bovell decided to remain permanently in the West Indies, and Osler left for Montreal with a heavy heart; but Bovell's absence made it easier for him to leave Toronto. "I lost a father and a friend," Osler said later; "but in Robert Palmer Howard, of Montreal, I found a noble stepfather, and to these two men, and to my first teacher, the Reverend W. A. Johnson of Weston, I owe my success in life—if success means getting what you want and being satisfied with it."

II

The McGill Medical School, founded by a Scot and using the methods employed in Edinburgh, was the best medical school in Canada, and only Philadelphia in the United States rivalled Montreal in the variety of diseases and the facilities for their diagnosis and treatment. And as for assets on the part of the Montreal General Hospital, Osler says that there were two in the old coccus-and-rat-infested building that was in such close touch with the school: much acute disease and a group of keen teachers. Pneumonia, phthisis, sepsis, and dysentery were rife. Students were given unusual freedom in the wards, serving as dressers, clerks, and sometimes, in serious cases at night, as nurses. The thoroughly successful pupil—called "the most promising student of the year" and "as good as he is clever"—studied in outpatient clinics as well as in the wards, getting much practical experience and writing a paper for the *Canadian Medical and Surgical Journal* based on cases he had studied. Although not a gold-medalist in his graduating class in the spring of 1872, he did receive an honorable mention that was unusual: "The Faculty has in addition this session awarded a special prize to the Thesis of William Osler, Dundas, Ontario, which was greatly distinguished for originality and research, and was accompanied by 33 microscopic and other preparations of morbid structure, kindly presented by the author to the museum of the Faculty."

An opportunity to achieve the goal of every new-fledged Canadian M.D.—a period of postgraduate study abroad—presented itself to Osler shortly after his graduation when his brother Edmund, who needed a companion on a visit to the relatives of his fiancée in Scotland, offered to pay the thousand dollars necessary for William's stay in Europe. Thus, the critical situation arising out of the temptation to go into immediate practice to fill his almost empty purse was averted by the first of his long series of trans-Atlantic journeys. On July 3, 1872, he sailed for Europe to spend two years at foreign universities. After visiting Dublin, Glasgow, and Edinburgh, he finally landed in London, where he spent about seventeen months in the Physiological Laboratory of the famous Englishman, Professor John Burdon Sanderson at University College. Here Osler studied histology and physiology and in the hospital saw the English system in operation, "with the hard work done by the student himself the essential feature," and although he was not a student in the hospital itself, he did have an opportunity to see well-known clinicians working and teaching.

Meanwhile, the bibliophile spirit began to smoulder in him as he took to visiting antiquarian bookshops. His inkpot career too was progressing, for a paper on some of his experiments was read in May, 1873, before the Royal Microscopical Society.

The paper later was published in the organization's *Quarterly Journal*, and Osler was invited to become a member of the Society. Intensive work in the physiology of the blood led to his discovery of blood platelets, perhaps, it is said, "his most important contribution to knowledge." Not only did Sanderson present to the Royal Society these original observations and discoveries which play an important part in the phenomenon of bloodclotting, but the good news reached Montreal, where Palmer Howard had this to say:

> In connection with this new subject of scientific interest, the older students present, as well as my colleagues, will be pleased to hear that Dr. Osler, who graduated here in 1872, has just made a discovery of great interest, and that promises well for the future of our young countryman. . . . I wish that some friend of this University would endow a Chair of Physiological and Pathological Histology, and that our young friend might be invited to accept the appointment and devote himself solely to the cultivation of his favourite subject, and at the same time bring honour to himself and to Canada.

Before leaving England for the Continent, Osler followed the advice of Palmer Howard and took his licentiate at the Royal College of Physicians in the fall of 1873. (Five years later he was to take examinations and be granted full Membership, that he might write M.R.C.P. after his name.) Three months in Berlin, followed by an equal length of time in Vienna, almost all of it devoted to work, and a return to Burdon Sanderson's laboratory—with this, his student days were at an end.

III

"Speck in cornea . . . 50c" is an entry in William Osler's account-book that he used to point out smilingly to future physicians: it was his first fee as a practising physician, entered shortly after his return to Dundas from abroad. Also, tradition has it that "for the consideration of $25 and a pair of old-fashioned elastic-sided boots which had proved too small for Charlie O'Reilly," he served as substitute for Dr. O'Reilly, who was Resident Physician at the City Hospital in Hamilton. But such things lasted only a short while, for on July 6, 1874, Dr. Palmer Howard wrote that Osler had been appointed Lecturer upon Institutes of Medicine at McGill, succeeding Dr. J. M. Drake. Howard added: "Please present my congratulations to yr father upon this gratifying recognition of yr merits by the oldest medical school in Canada."

The new professor was off to Montreal in August. Groaning heavily over the preparation of formal lectures, which he called a "ghastly task," he nevertheless began at the outset to make a good impression on his students, one of whom says that "From that hour physiology was an attractive study and the lectures like unto the Gods." The period was apparently the beginning of a renaissance for McGill; and with Osler as the moving spirit among a group of young and energetic medical professors of the highest standing, the result was a great reputation for all concerned. Osler's associations also took him beyond the college. Mainly through his brother, he became well acquainted with a group of financiers and railroad men who were at the time opening Canada's great western country to economic exploitation. From these men of affairs he acquired whatever worldliness he ever possessed, and incidentally secured their cooperation and often financial assistance in many

public health movements. He also helped to form a monthly dinner club among faculty members, and in the relaxed and often hilarious atmosphere of the club meetings his life became well rounded.

At the end of the term, Osler was appointed to Dr. Drake's chair as Professor. In May at the annual convocation, he made his first effort in giving the valedictory address to the graduating class. Cushing, in his magnificent biography of Osler, says that while the address does not contain "the literary quality which gave the charm to his later addresses," it is an epitome of things he continued to dwell upon more and more emphatically as the years progressed: that the graduates must continue always to be students; they must cultivate books, attend societies, cooperate with the journals; that their behavior is more important than "a string of diplomas;" and as Sir Thomas Browne writes, "No one should approach the temple of science with the soul of a money-changer."

Osler's industry, even from the beginning, was prodigious; so now, in the summer, in addition to his other work, he volunteered for work in the pathologic laboratory, where he came to be looked upon as the one to perform autopsies. Eventually, the post of Pathologist was created for him. Furthermore, needing money for microscopes in his department, he undertook work for a salary in the smallpox wards of the Montreal General Hospital. In this ill-lighted, ill-ventilated institution of about 150 beds, the task Osler undertook was disagreeable and also dangerous. But the epidemic during the summer of 1875, malignant as it was—and Osler, too, became ill with the disease in a very mild form—nevertheless gave an excellent chance for observation of clinical material. Osler made the most of this clinical and pathologic material for purposes of publication. Out of this summer's experience grew many things: papers on the pathology of the miner's lung, on smallpox, on vaccine, on smallpox rashes, and on the virulent haemorrhagic form of the disease; and in addition he came to feel that laboratory apprenticeship was the only way to learn much about medicine, that the best approach to teaching was in the pathologic laboratory, the postmortem room and the wards. When the Medical School reopened in the fall, although all that Osler was able to add was a chance for his students to become practically acquainted with the use of the microscope in physiology and pathology, this in itself was a great step forward—McGill being the first school in the country to offer such a course.

He now began to study morbid anatomy with great seriousness, a study which was to continue intensively for the next 13 years. The time spent in Europe under Virchow, and that spent long ago as a boy with the microscope, was being fully benefited from now. From May 1, 1876, to May 1, 1877, 100 autopsies were fully worked up, and Osler's manuscript notes fill three large quarto volumes, the cases all numbered and indexed—truly, as Cushing says, "a monument to his genius—his capacity for work." In his classes at McGill, many of his senior students took advantage of an opportunity that had been lacking formerly, three or four even getting a chance to perform autopsies; and back in class the specimens from these autopsies were discussed, questions asked, and problems cleared in an informal way. Also, Osler prepared for each student in attendance four to eight pages describing

each specimen, and in this way—though it made a heavy demand on his time—his teaching was of the greatest value. Is it any wonder his students loved him so?

As if all this weren't enough, we see in January, 1877, that he has another title: "Professor of Physiology in the Veterinary College, Montreal" and "Vice-President of the Montreal Veterinary Medical Association;" that he continued to work on his zoologic studies; that he was still interested in comparative pathology; that he talked before various medical societies; that he continued to make the results of his work available to his colleagues by publishing papers in the medical journals; and that he was watching the development of medical education with a keen eye. Indeed, he spent a week in Boston during April recess at the Harvard Medical School, where sweeping changes were under way, studying new methods and discussing medical education with members of the faculty there.

Osler's long hours and painstaking work in the postmortem room of the Montreal General Hospital and his clinical work during the smallpox epidemic began to pay dividends, for in May, 1878, he was appointed Physician to the hospital over the heads of the assistant physicians. This seemed scandalous to Osler, who had not gone through the usual apprenticeship as physician to outpatients; but the Board of Governors knew their man, and they must have been influenced not so much by the usual testimonials as by a petition from the students. He fully justified the faith and enthusiasm the students had in him, as witness this account by one of them on Osler's becoming Physician at the M.G.H.:

> When therefore his time came to take charge of a section of the hospital, older doctors looked on with bated breath, expecting disastrous consequences. He began by clearing up his ward completely. All the unnecessary semblances of sickness and treatment were removed; it was turned from a sickroom into a bright, cheerful room of repose. Then he started in with his patients. Very little medicine was given. To the astonishment of everyone, the chronic beds, instead of being emptied by disaster were emptied rapidly through recovery; under his stimulating and encouraging influence the old cases nearly all disappeared, the new cases stayed but a short time. The revolution was wonderful. It was one of the most forceful lessons in treatment that had ever been demonstrated.

What is all the more remarkable about this is that here was a young man of 29, revolutionizing almost the whole operation of a hospital before the very eyes of the older directors, which must have taken much boldness, self-assurance, and confidence. He hated medicines and believed too many drugs were being used—they called him a therapeutic nihilist—and he proved that the natural tendency of disease is towards recovery, if the patient is properly cared for, nursed, and not overdosed with drugs.

Beginning in the summer of 1879, Osler for the first time taught his students in the wards at the bedside, and for the next five years he divided his teaching between physiology and pathology in the winter term and clinical medicine in the summer. Concerning Osler's work as a pathologist, Harvey Cushing has this to say about W.O.'s frankness over his own diagnostic errors:

> If anything was disclosed which had been overlooked or misinterpreted he particularly dwelt upon it and called everyone to see. Then as regards the mistakes of others he had none of the sly delight which many pathologists have evidenced in "showing up" at the autopsy table the opinions of their clinical colleagues. A remarkable story is told, indeed, of how, to spare a surgeon's feelings, he concealed the

truth regarding a bad operative error. When this incident was recalled by someone in his presence many years later, Osler hesitated and then said: "He never asked me for a definite written report. In fact, no one but you and I ever knew of the unfortunate circumstance—and we have both forgotten it."

The most important event of 1881 was the International Medical Congress held in London under the presidency of Sir James Paget. Among the 3,000 who attended were Osler and R. Palmer Howard. The really epoch-making discussion of the congress was stirred up by Pasteur; what he had then to say about vaccination and the transmission of disease had much to do with the course of preventive medicine in the years to come. Violently opposed to the then widespread theory of spontaneous generation of germs in disease tissue, the great Pasteur supported the idea that "life comes only from life." He was upheld by most of the great names in the medical world who were at the congress: Paget, Lister, Virchow, Koch, Tyndall, Huxley, Darwin, Jenner, Langebach, Charcot, Volkmann. Because he felt his knowledge of bacteriology was too slight and possibly because he admired the English physician Bastian, who disagreed with Pasteur, Osler was almost indifferent to the importance of the subject. However, when he later came to make many tests, he became convinced that Pasteur was right. Osler's own paper on endocarditis was at least good enough for Dr. S. W. Gross, son of the then dean of American surgeons and expresident of the congress, to report to his father that Osler gave one of the best reports at the meeting and that he hoped they might get the man at Philadelphia some day: a day that was soon to come.

Back in Montreal, Osler's work in veterinary medicine on the study of parasites in the pork supply, presented before the Board of Health, was a great contribution to the health and hygiene of the city. He showed the necessity of government supervision over the source of food supply, and how important meat inspection was. Because Osler was a medical man and not a politician, his words carried great weight. Another public service, which did not, however, reach the public for 20 years, had its beginning at this time. Koch, in 1882, made the most important discovery of the decade in medicine—the *tubercle bacillus*. And less than a month after its publication, Osler was able to demonstrate to his class the same organism in the lung of a man who had died from tuberculosis. But as Cushing says, though he was "quick to confirm Koch's discovery, his inexperience with bacteriological technique rendered him incapable of pursuing the subject further."

In June, 1883, he was elected a Fellow of the Royal College of Physicians, London—he was already a member—probably the oldest society of physicians in Europe, Henry VIII having granted its charter in 1518. Although Osler cared little for such things for himself, the journals of his native country called his fellowship "a distinction which few men of Dr. Osler's age attain and which is now held by only two resident Canadians of any age."

The next spring he was able to take a short vacation in Europe as a relief from the excessive drudgery of teaching and to see what improvements had taken place in medicine abroad. Because of its presaging of twentieth century developments, his letter commenting on the Semitic invasion of Berlin is worth quoting at length:

The modern "*hep, hep, hep*" shrieked in Berlin for some years past has by no means died out, and to judge from the tone of several of the papers devoted to the Jewish question there are not wanting some who

would gladly revert to the plan adopted on the Nile some thousands of years ago for solving the Malthusian problem of Semitic increase. Doubtless there were then, as now, noisy agitators . . . who clamoured for the hard laws which ultimately prevailed, and for the taskmasters whose example so many Gentile generations have willingly followed, of demanding where they safely could, bricks without straw of their Israelitish brethren. Should another Moses arise and preach a Semitic exodus from Germany, and should he prevail, they would leave the land impoverished far more than was ancient Egypt by the loss of the "jewels of gold and jewels of silver" of which the people were 'spoiled." To say nothing of the material wealth . . . there is not a profession which would not suffer the serious loss of many of its most brilliant ornaments and in none more so than in our own. I hope to be able to get the data with reference to the exact number of professors and docents of Hebrew extraction in the German Medical Faculties. The number is very great, and of those I know their positions have been won by hard and honourable work; but I fear that, as I hear has already been the case, the present agitation will help to make the attainment of university professorships additionally difficult. One cannot but notice here, in any assembly of doctors, the strong Semitic element; at the local societies and at the German Congress of Physicians it was particularly noticeable, and the same holds good in any collection of students. All honour to them!

A matter of more personal importance to him came up this summer of 1883: the appointment to the Chair of Clinical Medicine at the University of Pennsylvania. When the announcement of his appointment had been made, and Dr. Howard and the McGill faculty had tried in vain to persuade him to remain in Montreal, he was tendered all manner of tributes, appropriate resolutions, and farewell celebrations. Thus closed the Canadian period, in Osler's thirty-fifth year, and McGill lost what Dr. Howard called its "potent ferment." Harvey Cushing sums up the work of those seven years:

During the short span of years since his McGill appointment he had stirred into activity the slumbering Medico-Chirurgical Society; he had founded and supported a students' medical club; he had brought the Veterinary School into relation with the University; he had introduced the modern methods of teaching physiology; had edited the first clinical and pathological reports of a Canadian hospital; had recorded nearly a thousand autopsies and made innumerable museum preparations of the most important specimens; he had written countless papers, many of them ephemeral it is true, but most of them on topics of live interest for the time, and a few of them epoch-making; he had worked at biology and pathology both human and comparative, as well as at the bedside; he had shown courage in taking the smallpox wards, charity in his dealings with his fellow physicians in and out of his old school, generosity to his students, fidelity to his tasks; and his many uncommon qualities had earned him popularity unsought and of a most unusual degree.

IV

When William Osler came down from Montreal to begin his work at the University of Pennsylvania, the first impression of the students was that here was someone different from what they had been used to in the past—such professors as Stillé and Pepper, who stood for the best in their medical educational traditions and ideas. Osler could, of course, be dignified, but cheerfulness and mischievousness were always breaking in. But the men who were responsible for Osler being in Philadelphia soon had reason enough to be proud and happy over their choice even if traditions had been thrown to the winds, for within a month of his arrival on the scene, where original research was almost unknown and facilities for it unavailable, Osler had rigged up a small clinical laboratory. Thus was produced "an atmosphere so encouraging and helpful that young fellows trooped to his side," and, as another of them said, it was like "a breath of fresh air let into a stifling room."

Helping to raise the educational standards in medical schools, a work in which the University of Pennsylvania was following President Eliot at Harvard; doing his best to cultivate friendships among physicians and professors; working continually with his students and by himself in the laboratories and wards of University Hospital and in the "dead house" at Old Blockley—in these ways Osler participated in all the phases of medical life in Philadelphia. He became, too, a member of the Philadelphia Neurological Society, over which Dr. Weir Mitchell presided, and from the material gained in the Philadelphia Hospital he wrote two monographs on nervous diseases of children. No less than 39 papers on every phase of clinical medicine came out of the stay at Pennsylvania, many of them directly from postmortem studies made at Blockley.

It was in Old Blockley, former alms house adjoining the University Hospital, where Osler was constantly found with a group of students around him, and more especially in the little red half-way house between the Blockley Hospital and Potter's Field, that opportunity was greatest for postmortem work. Often the official pathologists were busy elsewhere, and the old servant in "the dead house," knowing of Dr. Osler's enthusiastic and insatiable curiosity about disease, would call him immediately examinations were waived. Finally, Osler received a Blockley appointment. As Cushing says, "Many of the labours engaged in by physicians in the dissecting-room are repulsive enough, and those of the dead house still more so, for there are tasks to perform which a chambermaid or stable-boy would shrink from doing." Yet, with nothing but a storage vault and the small room with its stone table, and every possible inconvenience, no chance to perform an autopsy was ever lost. The records show 162, in Osler's handwriting. These postmortems supplied him with the material he needed to demonstrate his lectures, and the specimens were carefully studied under the microscope.

Osler's skepticism regarding the use of drugs shocked staid Philadelphia doctors. He preferred a "mixture of hope and nux vomica," while the eloquent and highly regarded oldtimers were recommending a dozen different drugs in the treatment of disease. But the internes knew that Osler "was a very good therapeutist . . . and used drugs not empirically but scientifically, and in his teaching laid great stress upon the general management of the disease."

In London early in the Spring of 1885 Osler gave, as the Goulstonian Lecturer of the Royal College of Physicians for that year, the first comprehensive account in English of "Malignant Endocarditis," an acute valvular disease of the heart. His lectures in the 250 year old series were warmly received, to judge from one who heard him and could "scarcely keep his seat, with emotion." Among other lectures that he gave during this year was "The Growth of a Profession," delivered in September at the annual meeting of the Canadian Medical Association, of which he was president. In this he dealt with the problems which preoccupied him all his life: the preliminary education of a doctor, the regulation of the medical curriculum, raising requirements for admission to medical schools, lengthening the course, establishing a licensing bureau, supporting boards of health, and attendance at meetings of medical societies. His literary activities for the same months include 30 editorials and 9 book reviews in *Medical News*, and one of the most important

sections in Dr. Pepper's five volume "System of Medicine"—diseases of the blood, of the blood-glandular system, and an 85 page treatise on the heart.

Almost everything that Osler did seemed eventually to develop into an article for a medical journal, a chapter in a textbook, a lecture which was reported, or notes and comments in his daybooks. He would dash off from a visit to his relatives in Canada to see or make a postmortem and find a rare disease that would subsequently be written up. He made full notes of such cases at Blockley as especially interested him, and then spent hours over the microscope with specimens obtained.

Osler *Bettman Archive*

William Osler (right foreground) with his students at a postmortem examination in Old Blockley Hospital, Philadelphia, 1887.

Though it is evident that he worked with intense concentration, it is amazing that he was able to take such an active part in so many organizations and still find time for long holidays; and even on these, he got grist for his literary mill. As he said later, "Both pen and brain got a deal of practice in Philadelphia." And not only did he himself turn out work, but by his example and his contagious enthusiasm, Osler stimulated those who came in contact with him to observe, record, and publish.

On October 3, he wrote Dr. William Pepper that he had received a definite offer from the Johns Hopkins Hospital and had determined to accept it. He was to move to Baltimore the following May. The new position meant much to him, for it marked a new departure, he said, in medical education in this country:

> It was not the hospital in itself, as there were many larger and just as good; it was not the men appointed, as there were others quite as well qualified; it was the organization. For the first time in an English-speaking country a hospital was organized in units, each one in charge of a head or chief. . . . The clinical unit of a hospital is the exact counterpart of one of the sub-divisions of any great hotel or department store.

On May 1, 1889, he delivered his valedictory address to Pennsylvania students, among whom he had deepened his understanding of the science and art of medicine

and where his broadened experience had perfected him for the great work he was to do in Baltimore. This brief address, whose title he later took for his volume of essays, *Aequanimitas*, dealt with two elements which he believed should keynote the lives of the students in their later days of success or failure: imperturbability and equanimity. Of the second quality Osler said:

> Let me recall to your minds an incident of that best of men and wisest of rulers, Antoninus Pius, who as he lay dying . . . summed up the philosophy of life in the watchword, *Aequanimitas*. As for him, about to pass *flammantia moenia mundi* (the flaming ramparts of the world), so for you, fresh from Clotho's spindle, a calm equanimity is the desirable attitude. How difficult to attain, yet how necessary, in success as in failure.

V

It was in the manner reflected by this story that Baltimore faced the new university and hospital that were built and grew up in the Maryland city:

"Where is the Johns Hopkins?" a stranger asked an old negro.

"It ain't anywhere's, sah! Just a lot of queer gentlemen going about; but they don't do nobody no harm, tho' some of them is ijuts with long hair!"

Having been left seven million dollars in 1873 by the will of Johns Hopkins, the Baltimore Quaker, merchant, bachelor, and believer in a university to train youth and a hospital to relieve suffering, the board of trustees had chosen as leader the president of the University of California, Daniel Coit Gilman. In 1876 the Johns Hopkins University was opened in good Quaker fashion without benefit of music, prayer, or benediction; and as if that were not enough for the citizens of Old Baltimore, Thomas Henry Huxley, the evolutionary biologist, delivered the inaugural address. Thirteen years later—it took all that time for constructing the buildings on the "pavilion" style (an outgrowth of the system of separated wards) and for the selecting of a staff—there was still considerable local hostility. This feeling was not mitigated by Gilman's refusal to prefer Maryland men or Southerners to those from other sections of the country. Backed by the trustees, Gilman chose a group who early brought to the university great fame abroad as a mecca for brilliant young scholars seeking inspiration and post-graduate study.

It was Dr. John S. Billings, as medical advisor to the Hospital, who planned the buildings and lectured about the Hospital and future Medical School, while Gilman was consulting men of the highest standing in medicine and scholarship. Though financially independent of one another, the University and the Hospital were to function in close cooperation, and from 1883 to 1889 the provisional medical school gradually came to resemble an institute of experimental medicine. The formal dedication of the Hospital in 1889 was widely heralded. For Osler, the beginning of such a place as this was a realization of a heartfelt ideal:

> To blaze a perfectly new road, untrammelled by tradition, vested interests, or medical "deadwood"—best of all, backed by a board of management imbued with a fundamental and abiding respect for scientific opinion and commanding an ample budget—what more could the heart of man desire?

Until the medical school could actually be opened—and this was to take five years—there was much planning to be done in regard to bedside clinical teaching,

with the emphasis on practical instruction to small groups of students who were already M.D.'s, but were pursuing their studies further at the Hospital. Osler, as chief of the Medical Department, used his knowledge of the German clinics to establish a hierarchy of long-term hospital residencies in place of brief internships; and as Dr. Welch had the chair of Pathology, Osler gave up his work in the laboratory and devoted himself to clinics. Of this he said later:

> If I have done anything to promote the growth of clinical medicine, it has been in this direction, in the formation of a large clinic with well organized series of assistants and house physicians and with proper laboratories in which to work at the intricate problems that confront us in internal medicine. For the opportunities which I have had at Johns Hopkins Hospital to carry out these ideas I am truly thankful.

It took young men to bring about the reforms that the Hopkins wanted: Dr. Osler, the senior in years, was not quite 40; Dr. Welch, a year younger; Dr. W. S. Halsted, the surgeon, 37; and Dr. Kelly, the gynecologist, only 31. It was these four men, immortalized later in a great painting by John Singer Sargent, who became famous as the Big Four at Johns Hopkins. Always active in organizing societies and keeping them going for the good of the profession and the advancement of the members, Osler met with the Hospital staff on the first and third Mondays of the month, when papers were read and interesting cases were discussed. The Journal Club was started; the first number of the *John Hopkins Hospital Bulletin* was issued; and the Historical Club was established at this time by Osler, Billings, and Welch. A visitor to Hopkins at this time is quoted as saying the new place so much talked about reminded him of a monastery, "with the unusual feature that the monks did not appear to bother their minds about the future."

About this time, in the course of a lecture Osler gave in Philadelphia, he told his listeners: "Given the sacred hunger and proper preliminary training, the student-practitioner requires at least three things with which to stimulate and maintain his education, a note-book, a library, and a quinquennial brain-dusting." Osler himself always carried a note-book, continually recording in it briefs of his thoughts or items of information, keeping an incessant watch for data of all sorts. He worked also, not only to build up his own library, but to bring into good use libraries in places where he worked. Now in Baltimore, he resurrected from its disuse and almost abuse in the basement of the Maryland Historical Society the library of the Medical and Chirurgical Faculty of Maryland, got for it decent quarters, and saw to it that the number of books was increased from a few hundred to over 15,000 before he departed for other shores in 1905. Of Osler's work along this line Welch has said: "It may, I think, be safely predicted that history will preserve Osler's fame as a serious and scholarly student of medical history and as a bibliographer as only second to his repute as a great clinical teacher." As for the third stimulant to education, the "*quinquennial brain-dusting*," W. O. spent much of the summer of 1890 in Europe, visiting Heidelberg, Strasburg, Munich, Paris, and elsewhere. In Paris he heard Koch's address on bacterial investigation, in which tuberculin was announced as a cure for tuberculosis; and on his return to Hopkins, he made some clinical tests with tuberculin. Tuberculosis, along with typhoid fever and pneumonia, was to hold Osler's interest more than other diseases, perhaps because of the questions of public health involved. He became the champion of public-health

measures and formed with his co-workers a society for the study of tuberculosis calling it "The Laennec" in honor of the famous French inventor of the stethoscope, who himself had studied the disease. If it is true, as some say, that Osler's work as a propagandist of public health measures was his greatest service to his generation, then a work that he began at this time was the one along these lines that will live for some time to come—his *magnum opus, The Principles and Practice of Medicine*, which was to go through edition after edition, to be translated into several foreign languages, and to become a medical bible to students the world over.

While the text book was shaping up under his hands, Osler received two offers from rival schools, the Jefferson Medical College of Philadelphia and Harvard Medical School. But another and more personal matter preoccupied him. When the *Practice* was finally completed, Osler is said to have visited Mrs. Samuel Gross, the widow of his old Philadelphia friend, tossing a copy of the big red book into her lap, and remarking, "There, take the darn thing; now what are you going to do with the man?" They were married in May, 1892, and then were off for Toronto and Montreal to see the Osler side of the match, and to Boston to see the Revere relatives; then a few days in Philadelphia, to Baltimore on business, to Washington for an address, and at last abroad, for the man of whom his wife had been warned that he "had books all over the floor" and the woman of whom one biographer says, "Dr. Osler's phenomenal luck reached its highest point when he married."

That fall of 1892 saw Osler at the opening of the medical buildings of the University of Minnesota where he spoke on "Teacher and Student." He spoke of the new ideas in medical education and berated an old order which permitted "a criminal laxity in medical education unknown before in our annals," and he said that "the inherent, vital element, which transcends all material interests, which may give a school glory and renown in their absence, and lacking which, all the 'pride, pomp and circumstance' are vain—this vitalizing element . . . lies in the men who work in its halls, and in the ideals which they cherish and teach." He warned the faculty not to have too many old professors on the staff and suggested that those of "riper" years ought to live "with the third decade, in company with the younger, more receptive and progressive minds." He spoke to the Minnesota Academy of Medicine on another subject close to his heart: his objection that the doctorate in medicine carried with it the licence to practice. Osler had insisted again and again that something be done about the laxity of registration in the United States, and he wanted a board—apart from college faculties—to hold examinations, set medical standards, and control admission to medical practice on the basis of capability. It was a reform he lived to see carried out in nearly all the states.

Nearer home there were other talks to be given, papers to be written, and more calls to other fields. McGill was again trying—no matter what the cost—to lure Osler back to Montreal. But money for its own sake interested him not at all; opportunity for effective work was what he sought. Meanwhile, through a benefaction of $300,000 from Miss Mary Garrett, who only insisted that women be admitted on the same basis as men, the medical school was able to open soon after the start of the new year, retaining both Welch and Osler who, it was feared, might have got away to some other school had there been further delay at Johns Hopkins.

GENERAL PRACTICE CLINICS

This new monthly section of General Practice Clinics features reports of papers delivered at current medical meetings in the United States and abroad.

Intraarticular Hydrocortisone in Rheumatoid Arthritis

Presented by IVAN F. DUFF, M.D., WILLIAM M. MIKKELSEN, M.D., WILLIAM D. ROBINSON, M.D., AND NOEL H. CHATELIN, M.D., before the American Rheumatism Association, San Francisco, June 18, 1954.

Over a three year period, 1,020 serial injections of 37 to 50 mg. of hydrocortisone were made into 105 rheumatoid joints of 60 patients. In 53 joints, worth while benefit was achieved; in 10 knees the injections were combined with orthopedic measures to overcome flexion contractures. In 15 other joints, benefit was eventually prolonged for 17 to 34 days before repeat injection was required. Upon discontinuation of therapy, benefit persisted from 4 to 12 months in 19 per cent of all treated joints. In 12 knees (7 patients) local remission of active inflammation accompanied improvement in untreated joints. Control of the arthritis in the knees of two patients, with maintenance of weight-bearing may have contributed to rapid hip-joint deterioration. Treatment of 32 joints was eventually discontinued because of partial initial benefit could not be further improved. Decreasing local responsiveness to the steroid was observed in 4 joints. In 20 joints there was no clinical response to hydrocortisone. Ten individuals refused repeated injections because of discomfort or failure to achieve worth while benefit. Synovial fluid from 35 knees was repeatedly studied. As previously reported, local hydrocortisone may produce remarkable alterations toward normal in joint fluid.

The Local Action of Growth Hormone on Granulation Tissue Formation

Presented by R. B. STEBBINS, PH.D. AND H. C. STOERK, M.D. (Merck Institute for Therapeutic Research, Rahway, New Jersey) before the annual meeting, American Association of Pathologists and Bacteriologists, Philadelphia, April 8–10, 1954.

An experiment on the effect of growth hormone on wound and granulation tissue was reported. Sterile cotton pellets containing cortisone and/or growth hormone were implanted on one side of an animal; a saline control was placed on the other side. After five days the extent of granulation tissue formation was

measured. The results were: growth hormone, 109 mg.; growth hormone and cortisone, 96 mg.; cortisone, 79 mg.; control, 90 mg.

Other substances tested were tissue extracts from brain, lung, kidney, heart, etc. It was found that extracts of the pituitary caused the most growth of granulation tissue. Furthermore, normal amounts of granulation tissue were formed by adrenalectomized and hypophysectomized animals. Therefore, the presence of adrenal or pituitary was thought not essential for the development of a normal body response.

The authors reached the conclusion that cortisone depressed the growth of granulation tissue, while the growth hormone very much increased it. Cortisone and the growth hormone were found to counteract one another.

The effects of these hormones on wound healing were also studied. Wounds, which normally took 13 days to heal, healed in 10 days with the use of growth hormone.

Treatment of the Usual Case of Poliomyelitis

Presented by R. CONNON ELEY, M.D. (Harvard Medical School) before the Symposiums on Poliomyelitis, Children's Medical Center, Boston, March 23, 1954.

The harmful effects of over-zealous treatment were emphasized. These include the unnecessary transport of the patient to the hospital when there is no need to hurry; this tires the patient and increases the likelihood of paralysis. The same can be said of chilling and frequent manipulations and examinations. The repeated injections of various drugs are also harmful and contribute to localization of the paralysis in the injected limb.

Positive measures require the cooperation of internist, pediatrician, orthopedist, physical therapist, psychiatrist, nurse, and social worker. The psychologic management of patients is extremely important. The prevention of contractures and deformities can be done by the orthopedist in detecting early changes and directing proper preventive measures. Bacterial infections must also be prevented, and for this the author uses penicillin and streptomycin parenterally to protect against pneumonia and other respiratory infections. Relief of pain and spasm can be achieved with application of hot pack.

Sedation should be used sparingly and cautiously and respiratory depressants should be avoided. Aspirin and codeine have proved satisfactory in the author's experience. Oversedation may mask respiratory failure. Fluid therapy should be somewhat restricted, and if the urine specific gravity is between 1.020–1.030, hydration is adequate. For bladder difficulties furmethide is recommended as the initial therapy. If this fails to relieve urinary retention, catheterization must be used and tidal drainage is the method of choice. In the author's view, chemotherapy of poliomyelitis is of no help. ACTH should not be used since it might convert an abortive or nonparalytic case into a paralytic or fatal one.

Diagnosis of Acute Poliomyelitis

Presented by LOUIS WEINSTEIN, M.D. (Boston University Medical School) before the Symposium on Poliomyelitis, Children's Medical Center, March 23, 1954.

In the absence of elaborate laboratory facilities, the diagnosis of poliomyelitis now rests upon the clinical history, physical examination, and course of the disease. There are three clinical groups of poliomyelitis: (1) abortive poliomyelitis; (2) nonparalytic poliomyelitis, and (3) paralytic poliomyelitis.

Abortive Type: In this group the signs and symptoms suggest disease outside the central nervous system and present as a variety of syndromes. One is that of a simple upper respiratory infection with fever, perhaps redness of the throat, coryza, and headache. The second is the gastrointestinal syndrome usually seen in older individuals and characterized by fever, malaise, generalized muscle and bone aching, and weakness. These patients develop viremia and may spread the disease to susceptible persons.

Nonparalytic Poliomyelitis: In this group there are symptoms of generalized infections plus evidence of central nervous system involvement. There is evidence of meningeal irritation, and cerebrospinal fluid is abnormal. Paralysis does not develop; however, it is important to realize that other diseases both in and outside the central nervous system can produce this train of events, viz., encephalitis, brain abscess, subarachnoid bleeding, meningisms, cervical arthritis, hysteria.

Abnormal spinal fluid is also not specific for poliomyelitis. When done early, the first lumbar puncture reveals a normal cerebrospinal fluid pressure, usually a normal protein content, and a slight to moderate elevation of cells. The cells are predominantly polymorphonuclears, and the sugar is normal or moderately elevated. During the next few days (usually two to four) a lymphocytosis occurs, the protein content of the spinal fluid rises, the sugar does not change. It sometimes happens at this stage that the cell count falls to normal. This together with the rise in protein may suggest the Guillian-Barre syndrome. It is reported that the spinal fluid may be normal in as high as 15 per cent of cases. This, in the experience of the author is much too high and the diagnosis of poliomyelitis must be held suspect so long as the spinal fluid is normal. This incidence would undoubtedly fall if careful re-examination of the spinal fluid were done at intervals.

Among the diseases that may be confused with poliomyelitis, the following are probably the most common: healing bacterial meningitis, mumps, the encephalitids, postinfections encephalitides, syphilitic meningitis, allergic reactions, multiple sclerosis, rheumatic fever (rarely), brain tumor, and a small amount of subarachnoid bleeding.

The paralytic variety of poliomyelitis is usually easily diagnosed and consists of the prodroma mentioned under the abortive type, plus signs of meningeal irritation, plus paralysis. However, the development of paralysis of the upper motor neuron type, or evidence of sensory loss, brings the diagnosis into question.

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INCORPORATING INTERNATIONAL RECORD OF OPHTHALMOLOGY

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Miscellaneous

Book Reviews

Announcements

A section entitled International Record of Ophthalmology is included at the beginning of the journal. The Record Section consists of advanced clinical and experimental reports.

Quarterly Review of **OPHTHALMOLOGY**

ABSTRACTS

OPTICS, PHYSIOLOGY, AND PSYCHOLOGY OF VISION

46. *The Discrimination of Subliminal Visual Stimuli.* F. W. R. TAYLOR. Canad. J. Psychol. *7*:12–20, 1953.

An anticipatory reaction to an electric shock was developed in human subjects by presenting a visual stimulus before the electric shock was given. The visual stimulus was then reduced to a subliminal level but the anticipatory reaction could still be found. A form of learning had taken place at a level other than the conscious.

The perceptual threshold may be raised or lowered before conscious appreciation is possible.

47. *The Pullman Study—A Visual Survey of Pullman School Children.* FRANCIS A. YOUNG, ROBERT J. BEATTIE, FRED J. NEWBY AND MARK T. SWINDAL, Pullman, Washington. Amer. Journal Optom. & Arch. Amer. Acad. Optom. *31*:111–121, March 1954.

The parents of the entire school population of 1,293 children in the college-farming town of Pullman, Wash., were asked to fill out an extensive questionnaire dealing with hours of near work, lighting conditions, posture, diet, sleep, diseases, etc., and to grant permission to have their children's vision tested. More than half of the parents responded by filling out the questionnaire yielding a population for testing of 652 children or just half of the total population of children from ages 5 through 18. A comparison of the population of parents responding with those not-responding indicated that more of those in the professional class and fewer in the unskilled labor class responded. The sample was thus composed of children from the following occupational groups: professional, 294; managerial, 59; sales and clerical, 41; services, 40; agricultural, 91; skilled labor, 53; semiskilled labor, 39; unskilled, 31; and unclassified, 4, yielding a total of 652 children. Since the investigators are primarily interested in a comparison of the children in the professional and agricultural groups, the question of the representativeness of the sample is of less importance.

The following findings were taken in an assembly line fashion with each of the six testers taking a certain group of findings on all the children: visual acuity, monocular and binocular at both far and near with and without prescriptions; eye-hand dominance; height, weight, elbow to finger-tip length, bizygomatic index,

reading distance, color vision, interpupillary distance, static and dynamic retinoscopy, red-green test, phorias and ductions at far and near, rotations and versions, external ocular exam, near point of convergence and ophthalmoscopic exam.

The results were coded, punched on IBM cards, and summarized with both point and moment statistics. The retinoscopic data were translated into equivalent spheres. A comparison of the test results between age groups by means of the F test indicated that there is no significant difference between ages on dynamic retinoscopy —OD and OS, recovery base out—far and near, lateral phoria—near, vertical phoria—far and near, and recovery base in—far. All other tests showed significant differences with age.

All the measures of far visual acuity and the measures of refractive error indicate a major change taking place at 10 years of age. The 10 year olds show a relatively large drop in visual acuity and an average minus refractive error on the red-green and static retinoscopy. The results obtained on Pullman school children were compared with those found by Hirsch and by Kempf, Collins, and Jarman. The usual increase in the incidence of myopia with an increase in age was found. This increase differs from that found by Hirsch in that the onset was earlier, about 9 to 10 in girls and 11 to 12 in boys. Also the percentage of cases showing a minus refractive error was about double that found by Hirsch (30 per cent as against 14.8 per cent for the total groups; 27.5 per cent for boys against 14.8, and 32.7 per cent for girls against 14.8 per cent). In terms of skewness of age distributions, a result similar to Hirsch's was found: the distribution of refraction is skewed toward the hyperopic side until the age of 9 or 10, is symmetrical at this age, and then becomes increasingly skewed toward the myopic side with increased age. Hyperopia increases from age 5 to 6 for both boys and girls and then decreases at higher ages. There are more boys than girls with myopia greater than one diopter in all age ranges between 5 and 14 except in the 9 to 10 age range. Girls had a higher percentage of myopia than boys. 4 tables.—*Author's abstract.*

PHYSIOLOGY, CHEMISTRY AND BIOCHEMISTRY OF THE EYE

48. *The Use of Radioactive Phosphorus* (P32) *in Differentiating Neoplastic from Other Intraocular Lesions.* I. J. EISENBERG, I. S. TERNER AND IRVING H. LEOPOLD, Philadelphia, Pennsylvania. Combined Meeting of Section on Ophthalmology with Association for Research in Ophthalmology. June 22, 1954.

To-date P32 concentration tests have been performed on 175 patients with various intraocular and extraocular lesions where malignancy could be one of the etiological factors.

In the authors' last report at the A.M.A. meeting in June, 1952, it was demonstrated that (1) a variation of 30 per cent or more from the average in the normal eye indicated either an intraocular neoplasm or inflammatory lesion. (2) Serous detachments showed a concentration of P32 under 30 per cent as compared to the average of the normal eye.

In an effort to differentiate between inflammatory and neoplastic intraocular lesions, the technic was modified to include a time graph concentration of P32. Readings were now taken at 1 hour, six hour, 24 hour, and 48 hour intervals, otherwise the procedure and calculations of the test remained the same as reported in the previous paper.

From the group of 175 patients, 104 were tested using the 1 hour, 6 hour, 24 hour, and 48 hour intervals. In this group 88 patients had intraocular lesions.

In analyzing our data the following conclusions appeared valid: (1) The P32 test should be considered positive if (a) in one hour the variation in the concentration of P32 is 30 per cent or more than the average in the corresponding normal eye. (b) In 24 hours this percentage variation must show an *increase* over the one hour percentage variation. (2) To-date only neoplastic lesions will give a positive P32 concentration with the above modification of the test.

Therefore, it is now felt that this modified P32 concentration test is of definite value in helping to establish the diagnosis of intraocular malignancy.—*Author's abstract.*

49. *Contamination of Eye Medications: Practical Methods of Prevention.* J. H. KING, JR., Washington, D. C. Am. J. Ophth. *36*:1389–1397, October 1953.

The sources of contamination of eye solutions and ointments, both during manufacture and clinically, are discussed. In order to minimize contamination, the author suggests that all pharmacies formulating and compounding eye medications be rigidly controlled. He advocates for solutions either small sterile refillable containers, disposable sterile containers, and the use of disposable plastic eye droppers. The latter are believed most practicable for clinic and office practice. As fluorescein solution is a good culture medium for *pseudomonas aeruginosa*, sterile dried fluorescein, either impregnated in filter paper or as a small compressed wafer, can be used in lieu of disposable droppers. Suggestions as to minimizing contamination of ointments include discussion of disposable sterile paper rods to be used as individual applicators, disposable extension tubes on ointment containers, and use of miniature tubes. 17 references. 5 figures.—*Author's abstract.*

50. *The Uses and Abuses of Adrenal Steroids and ACTH in Ophthalmic Diseases.* MICHAEL J. HOGAN, PHILLIPS THYGESON, AND SAMUEL KIMURA. Presented at the 90th annual meeting of the American Ophthalmological Society, June 16–18, 1954, at Glacier Park, Montana.

Concerning topical therapy the authors made the following observation in regard to blepharitis and blepharoconjunctivitis: Seborrheic blepharitis is improved by topical therapy. If it is associated with an infection, a combination of adrenal steroid plus an antibiotic is of help. Keratoconjunctivitis, associated with atopy, acne rosacea and contact dermatitis responds to local treatment. Hydrocortisone and cortisone are equally effective, except in seborrhea where hydrocortisone is more helpful.

The authors believe that there is no advantage in combining antibiotics with adrenal steroids for the topical treatment of infectious conjunctivitis. In suspected trachoma, as a provocative test, steroids are of definite value. Vernal conjunctivitis most often responds to hydrocortisone. Allergic dermatitis and conjunctivitis repond poorly to cortisone, but the response is better to hydrocortisone. Phlyctenular conjunctivitis subsides promptly on treatment with either steroid. Diffuse episcleritis responds in approximately 50 per cent of cases to treatment with both steroids. Nodular episcleritis is not benefited.

Regarding the treatment of corneal diseases, the authors state that suppurative inflammations are not benefited by combined steroid and antibiotic therapy. Phlyctenular keratitis responds dramatically. Vascularization is seemingly prevented in interstitial keratitis. Herpes febrilis infections should not be treated with adrenal steroids in the active or metaherpetic phase. Systemic administration of antibiotics may result in monilia and other fungus infections in patients with herpes of the cornea. Topical hydrocortisone may result in the development of dendritic keratitis. Subconjunctival injection of steroids may be of value in cases resistant to topical therapy.

In the treatment of intraocular inflammations, the authors state that acute iridocyclitis is benefited in 75 per cent of cases. Chronic iridocyclitis is benefited by slightly. Choroiditis is not helped by topical or subconjunctival treatment.

Inducing systemic therapy the authors point out that cortisone may be given orally or intramuscularly. Hydrocortisone (free alcohol) is effective orally and on intramuscular use. ACTH may be given either intravenously or intramuscularly. Systemic treatment is of the most value in diffuse inflammations, cases resistant to topical therapy, in choroiditis, optic neuritis, and orbital inflammations. Intravenous ACTH may be given in acute cases where the macula and papillomacular bundle are endangered.

Steroids or ACTH should not be administered to patients with diabetes, peptic ulcer, hypertension, and pulmonary tuberculosis.

OCULAR MOVEMENTS AND MOTOR ANOMALIES NYSTAGMUS READING DISABILITY

51. *The Prescription of Visual Training by a Graphical Method.* V. J. ELLERBROCK. Am. J. Optom. & Arch. Am. Acad. Optom. *30*:559–568, November 1953

This paper reviews the mathematical and optical theory of the Brewster stereoscope as an orthoptic instrument and the prescription of visual training with a stereoscope and Donder's graphical method. The general equation for computing the prismatic effect from the orthoptic positions of the targets is presented. Several examples then are provided for illustration of the use of the equation. The basic design of the Donder's graph is described. On the graph, prismatic effects for different types of stereoscopes are plotted and related to various types of binocular imbalance.

It is pointed out how the use of the graphical method readily provides the pre-

scription of specific stereograms as well as the method of their employment by the patient. This eliminates doubt for the patient in carrying out home training procedures, and better enables the practitioner to evaluate the results of a training program.—*Author's abstract.*

52. *The Retraction Syndrome.* H. REED. Manitoba Medical Review. *34*:329–330, June 1954.

The retraction syndrome consists of retraction of the affected eye into the orbit and narrowing of the palpebral fissure on adduction, absence of adduction, and decreased range of convergence. A sixth nerve palsy can be differentiated because there is no retraction, convergence is not weakened, diplopia is present, and the condition is usually not congenital. In retraction syndrome, a squint present in the primary position, the eyes may be straightened by operation. Two cases are described. 3 references. 6 figures.

53. *The Correction of Diplopia after Fractures of the Orbit.* EDMUND B. SPAETH, Philadelphia, Pennsylvania. Tr. Am. Acad. Ophth. *57*:883–888, November-December 1953.

This article was a portion of a Symposium entitled "Malunited Fractures of the Zygoma." The continuation of diplopia after a fracture of the orbit, due either to displacement of the eyeball itself by reason of mechanical factors or due to nerve-muscle injury to the third or sixth nerve and to the muscles they innervate, is the most significant part of this problem. In addition, post-traumatic enophthalmos with consequent diplopia and posttraumatic immobility of the globe, a sort of cicatricial strabismus fixus with adhesions to the external canthal angle, must be discussed.

If early or immediate treatment of an orbital fracture is carried out properly, it is conceivable that diplopia will not remain as a permanent feature. This, however, is not the fact. It is true that an immediate complete reduction of a fracture's orbit will prevent later diplopia from displacement of the eyeball because of a depressed floor of the orbit, but it will not prevent that from a ruptured suspensory ligament, from sixth cranial nerve paralysis, or from a ruptured lateral rectus muscle. In addition to these, subtotal third nerve paralyses are not uncommonly seen, ptosis is not too uncommon, and even a complete third nerve paralysis has been seen with a later pseudo-Graefe syndrome from misdirection of regenerating third nerve fibers.

Diplopia is not a certain diagnostic sign of a fractured orbit, i.e., the maxillary-zygomatic region. A sharp impact injury of sufficient force to cause a fracture may result in intraorbital hemorrhage and varying degrees of immediate oculomotor palsies, especially the lateral rectus muscle, the inferior rectus muscle, the inferior oblique muscle, and the levator muscle, in this order of frequency.

A paralysis of the external rectus muscle which remains unimproved for one year after the original trauma, when the paralysis is due to nerve involvement, should be operated upon after that interval of time with tendon transplants from the superior and inferior rectus muscles to the tendon of the paralyzed lateral rectus muscle.

The method of handling the medial rectus muscle during this surgery is somewhat important. If the patient can move the eye to the midline, a recession of the medial rectus muscle should be a secondary procedure. This should be done after the tendon transplants, perhaps five to eight days later. If, however, the patient cannot move the involved eye to the midline, then a recession of the medial rectus muscle should be done as a first procedure. If, following this procedure, the eyeball moves to the midline, it is perfectly proper to carry on with the tendon transplants, knowing that the results from the surgery will be worth while.

These cases also have, in addition to the pseudoptosis, varying degrees of true ptosis, especially at the outer canthal angle. The ptosis should be corrected by a classic levator resection.

Some of the methods available have been presented to emphasize the effort that must be put forth surgically for the correction of the diplopia because they are all involved cases. 5 figures.—*Author's abstract.*

ANOMALIES OF REFRACTION AND ACCOMMODATIONS, CONTACT LENSES

54. *Congenital Bilateral Coloboma of Iris and Choroid:* A Case Report. ROBERT GREENBERG. Am. J. Optom. & Arch. Am. Acad. Optom. *30*:631–634, December 1953.

The author reviews a case of congenital ocular anomaly that resulted in visual impairment that could not be aided by routine optometric or ophthalmologic technics. The report outlines the procedure followed to improve visual acuity through the use of subnormal visual aids. To offset the irregular shape of the pupil caused by the coloboma of the iris, a fluidless, scleral contact lens was painted with an artificial iris and fitted to the patient. Since the existing pupil was displaced nasalward, it was necessary that a special asymmetrical lens be designed to prevent rotation on the eye. There was no measurable error of refraction, but lack of normal retinal development made it necessary to also employ a telescopic lens. This apparatus, in conjunction with the contact lens, afforded an improvement in acuity from 20/100 to 20/40 and permitted comfortable reading at a normal distance.—*Author's abstract.*

55. *Image Magnification in Corrected Aphakia.* JOSEPH I. PASCAL, New York, New York. Eye, Ear, Nose & Throat Monthly. *33*:290–293, May 1954.

The usual teaching that the strong plus lens which corrects aphakia magnifies the image in that eye needs some clarification as it is not entirely correct. The lens magnifies strongly the "basic," unclear retinal image, but minifies slightly the clear "optical" image formed by the uncorrected aphakic eye. There are four images to be considered, and as Figures 1 and 2 show, the outside images, the smallest and largest, belong to the uncorrected aphakic eye. The middle 2 relate the original retinal image before operation and the retinal image after operation and correction.

The change in size between the first two and last two images is slight—about 4 per cent. The change in size between the middle two images is large—about 30 per cent. The correcting lens in aphakia, while it strongly magnifies the clear retinal image relative to the retinal image before operation, minifies slightly the clear optical image formed by the uncorrected aphakic eye. 1 reference. 2 figures. —*Author's abstract.*

CORNEA, SCLERA AND TENON'S CAPSULE

56. *A Three Generation Pedigree of the Blue Sclerotics Syndrome.* HARRY A. JANKIEWICZ AND LEO ZANKAN. Am. J. Optom. & Arch. Am. Acad. Optom. *30*:581–587, November 1953.

A historical review of the discovery and description of the blue sclerotics syndrome reveals that it has been called Spurway's, Eddowe's, Adair-Dighton's, and van der Hoeve's and de Kleijn's syndrome as well as hereditary hypoplasia of the mesoderm, congenital mesodermal dysplasia and hereditary mesodermal dystrophy. The term blue sclerotics syndrome is favored.

The authors' pedigree with four affected individuals in three generations can be explained by either simple or irregular dominant inheritance. The variable expressivity of the syndrome was demonstrated by a patient who had blue scleras only, another that had blue scleras and fragile bones, and 2 that had otosclerosis, fragile bones, and blue scleras. Middle ear deafness was the last symptom to appear, and it is most often detected between the ages of 20 and 40.

Studies are reviewed on the inheritance of the syndrome, and on histologic attempts to explain the color of the sclera. Observations of others indicate that blue-colored scleras are associated at times with myopia, keratoconus, megalocornea, hydrophthalmia, aniridia, and microphthalmia. 12 references. 2 figures.—*Authors' abstract.*

VITREOUS HUMOR

57. *A New Phenomenon Observed in the Anterior Vitreous Body in the Course of Uveitis (Un nouveau phénomène observé dans le corps vitre antérieur au cours des uvéites).* Archimède Busacca, Sao Paulo, Brazil. Ophthalmologica *126*: 355–360, December 1953.

Examination with the biomicroscope shows that normally the lamina plicata of Vogt is inserted circularly on the lens and forms the triangular retrolenticular space. Observations made in patients with severe uveitis have shown that in some cases, if the eye moves rapidly upward and downward, the opaque lamellae in the vitreous body undulate rapidly; but when the eye is at rest, instead of extending downwards under the influence of gravity, as is normal, they extend upwards. In such cases if the lamina plicata is still visible with the biomicroscope, it is seen that both the inferior and superior lamellae extend upward and the retrolenticular triangular space has become rectangular. As the inflammatory uveitis subsides,

the lamellae return to their normal position, and the triangular retrolenticular space is again clearly visible. This phenomenon, which the author believes has not been previously observed, is not seen in all forms of uveitis, but up to the present time he has not found any relationship between the etiology of the uveitis and the changes observed. 3 figures.

RETINA

58. *Retrolental Fibroplasia; An Ophthalmic-Pediatric-Obstetric Problem.* GEORGE M. HAIK, GEORGE S. ELLIS, AND TIMOTEO JIMENEZ, New Orleans, Louisiana. Louisiana State Medical Society. *106*:214–227, June 1954.

Retrolental fibroplasia, a disease of the retina which destroys the vision of premature babies, was an unknown and unnamed clinical entity before 1942. Today this disease is the commonest cause of blindness in infants and young children One of the strangest facts of its enormous increase in incidence is the concentration of cases in the United States in recent years. The regional distribution in this country is uneven, and the incidence varies from year to year under precisely the same circumstances of environment and management.

It was not until six years after the first case had been reported that it was found, by the observation of a large series of premature infants from birth, that the pathologic findings first reported represented an advanced stage of the disease. Actually, retrolental fibroplasia appears in three stages: (1) dilatation and tortuosity of the retinal vessels, the development of new vessels and the development of capillary varices; (2) the appearance of grayish localized or generalized retinal elevations and small retinal hemorrhages; (3) the extension of newly formed vessels and supporting tissue from the retina into the vitreous, with detachment of the retina. The extent of destruction in the final cicatricial stage depends upon the severity of the acute or active process and the amount of regression which occurs as activity subsides.

The one indisputable fact about the etiology of retrolental fibroplasia is that it is primarily a disease of prematurity. The first manifestations most often occur between the second and fifth months of life, though it is sometimes observed both earlier and later, and, very occasionally, in newborn children.

The causes which have been eliminated include constitutional factors; associated fetal defects; maternal susceptibility to abortions and premature births; complications of pregnancy such as pre-eclampsia and other toxemias, and bleeding complications; parental age, syphilis and Rh incompatibility; prepartal management and medication; maternal disease, nutrition and parity; fetal methods of feeding, time of weaning, and vitamin and other therapy.

The only investigation which has led to any positive results has to do with the theory of anoxia and oxygen therapy, but even it stands in need of clarification. Studies reported to date show that the excessive use of oxygen and its rapid withdrawal may cause the disease but also show that the use of oxygen may reverse the pathologic process that has occurred. No single, properly controlled series has been

large enough to be really significant statistically, and the various circumstances of management and other considerations make their combination impossible. The cooperative, well-controlled study, which will shortly be reported from a number of American hospitals, is expected to end these difficulties and to throw light upon this particular theory of the etiology of this perplexing disease.

The diagnosis of retrolental fibroplasia seldom presents any confusion. The differential diagnosis is chiefly concerned with persistent hyperplastic vitreous, retinal dysplasia and retinoblastoma. The disease will not be recognized, however, if it is not searched for promptly, by ophthalmoscopic methods, in all premature children and if the examinations are not continued serially for a sufficiently long period of time, preferably for the first nine months of life.

The only prophylaxis, in the present state of knowledge, is for the obstetrician to use every means at his command to forestall premature delivery. It is essential that he do so, for there is no definitive therapy for this disease. The most useful method of treatment is the use of mydriatics to prevent or control synechia-formation, which, in turn, may prevent secondary glaucoma.

At the present time retrolental fibroplasia is a matter of great concern in teaching hospitals and research centers. Otherwise, there is no general feeling of responsibility about it. Obstetricians and pediatricians tend to feel that the mere identification of the disease serves no useful purpose since there is no effective therapy. This is a defeatist point of view. It is true that at the present time retrolental fibroplasia is a matter of concern chiefly to the ophthalmologist, and that he can do little more than diagnose it. It must become the general concern of obstetricians, pediatricians, and epidemiologists. With their joint cooperation, it is inconceivable that, as has happened so often in other diseases, some method will not eventually be found to control and cure this grave complication of prematurity. 31 references. 2 figures.—*Authors' abstract.*

NEURO-OPHTHALMOLOGY OPTIC NERVE, VISUAL PATHWAYS, CENTERS AND VISUAL FIELD

59. *Ocular Abnormalities in Poliomyelitis and their Pathogenesis.* R. G. MURRAY AND F. B. WALSH. Canad. Med. Assoc. J. *70*:141–147, February 1954.

The small neurotropic polio virus has a constant attraction to the nerve cells. The primary change is first in the cytoplasm, and nuclear changes occur only after the onset of cytoplasmic chromatolysis. The first cellular inflammatory response is polymorphonuclear, but a mononuclear response quickly follows. Cells may be damaged and recovered but if edema is present most of the cells are destroyed. The process of cell destruction reaches its peak in three to six days; paralysis is maximum within the first week. The lymphocytic response tends to increase with convalescence and may remain for six months. The ratio of motor cells to motor nerves and muscle cells is high for the ocular muscles, therefore, a massive blow to the nuclei would be necessary to affect the ocular rotations.

The cerebral and the cerebellar cortex are rarely involved. The brain stem is

affected in three main areas: the reticular formation, the vestibular nuclei, and the roof nuclei of the cerebellum. The anterior horn cells, the posterior and intermediate horns, the posterior columns, and the sympathetic motor columns of the spinal cord may be affected. The visual cortex, the visual pathways, and the optic nerves are not affected.

Choked discs may develop in poliomyelitis. They may be due to increased spinal fluid pressure or may be related to the increased spinal fluid protein. Optic neuritis associated with polio has not been proved. A transitory visual depression may occur and is usually associated with extensive brain stem involvement.

Diplopia is a most frequent ocular symptom. The sixth nerve is most commonly involved, the third less frequently, and the fourth but rarely. Total external ophthalmoplegia occurs, without pupillary widening. Also palsy of conjugate movements can occur.

The seventh nerve may be involved, usually with the sixth nerve. There is no characteristic pupillary change in poliomyelitis. Horner's syndrome may occur.

Nystagmus is the commonest ocular complication, occurring with an ocular muscle palsy, with paralysis of conjugate movements, or in a pure form. The nystagmus may be lateral, vertical or rotatory.

The incidence of ocular complications varies widely in different epidemics: from 2.9 to 5.1 per cent. The ocular complications occur in 22 per cent of cases of bulbar poliomyelitis. Ocular signs are merely part of bulbar involvement and have no significance as regards mortality. 22 references. 1 table.

60. *Traumatic Lesion of the Optic Chiasma with Anterior Pituitary Insufficiency.* D. BOWERS. Treatment Services Bulletin, Ottawa. *8*:179–188, 1953.

The patient was injured in a street car accident and was unconscious for six hours. Following the accident he was blind, but regained the nasal field of vision of both eyes. He developed the signs of anterior pituitary insufficiency.

Roentgenograms showed a small pituitary fossa and thick clinoid processes. The symptoms of pituitary insufficiency disappeared when he was treated with thyroid extract, cortisone, and testosterone.

The vascular supply to both the chiasm and the pituitary probably was harmed by the injury.

GLAUCOMA AND HYPOTONY

61. *Bulbar Pressure Test in Glaucoma.* P. L. BAXTER. Brit. J. Ophth. p. 641, November 1953.

The author describes "a simple clinical test devised to estimate the facility of outflow of aqueous from the eye while external pressure is being applied to the globe."

He introduces two terms: (1) The first is "outflow fraction," which equals the fall of tension produced by compression of the eyeball represented as percentage

of the initial tension in given eye. At fall of tension author considers the difference between the reading taken 10 to 15 seconds after the application of the Bailliart dynamometer and another reading taken four minutes later (the tonometer is left on the cornea throughout the test). By taking the measurement while the dynamometer is in place, the author excludes from calculation, he believes, the difference between the amount of blood present inside the eyeball initially and after the removal of the dynamometer. (2) The other term is "optimum compression," which is the weight that produces the maximum value for "outflow fraction." Empirically this was established as 45 g in normal eyes. For practical purposes the author recommends 65 g. i. e. tonometer 15 g plus 50 g applied with dynamometer. This seems to accentuate the difference in facility of outflow in normal and glaucomatous eyes.

The test is of value mainly in early diagnosis of chronic simple glaucoma. The technic of the test is described, its application discussed, and a table for rapid calculation of results of the test is given .

62. *Notes, Cases, Instruments, A Correlation of Intraocular Pressures; With Microscopic Sections Following Cyclodiathermy on Normal Rabbits.* J. ALEXANDER VAN HEUVEN AND JAMES PHILIP DUNN, New Haven, Connecticut. Am. J. Ophth. *36*:1447–1449, October 1953.

Normal rabbit eyes were subjected to cyclodiathermy. The postoperative intraocular pressures showed an immediate and severe rise to levels from 59 to 70 mm. Hg, decreasing rapidly, however, so that four hours postoperatively all eyes were hypotonic. This low pressure continued for at least one week. In the nontreated eyes, there was also a marked fall in pressure.

Histologic sections show gross destruction of the treated processes with eventual scarring and atrophy. The nontreated processes show immediate uveal dilation with edema and hyperemia but return to normal by six days after operation. There is no hypertrophy of the remaining processes. 3 references. 1 figure.—*Author's abstract.*

63. *Angle-Closure Glaucoma: Subacute Types.* PAUL A. CHANDLER AND ROBERT R. TROTTER. Tr. Am. Ophth. Soc., 1954.

The authors state that in subacute angle glaucoma, as in acute, obstruction to flow from the anterior chamber is due solely to closure of angle; the filtration apparatus itself being normal. The clinical course of the subacute types differs from the acute form in that the episodes of elevated tension are more frequent, but less severe, than in the acute form. In the untreated or inadequately treated case, gradual cupping of the disc and loss of field ensue, as in open-angle glaucoma. In the early stages, before too much of the angle is permanently closed by peripheral synechias, peripheral iridectomy is completely effective in arresting the process. This operation plus miotic treatment will usually control the disease if a moderate amount of field loss is present. In the advanced stage only, a filtering operation will

suffice. Cases are reported illustrating the effects of medical and surgical treatment in the various stages of the disease.

64. *Treatment of Glaucoma with Hydergine.* L. P. AGARWAL, Agra, India. Ophthalmologica. *127*:3–33, January 1954.

Twenty-seven patients with various types of glaucoma were treated with hydergine. The tension was temporarily reduced in 19 cases irrespective of the type of glaucoma. One cc. of the drug was given I.V. three times a day for two days followed by 3 sublingual tablets a day for three to four days. The treatment was based on the view that glaucoma is a sympathicotonia. There are conflicting reports in the literature whether simple or congestive glaucoma is associated with a sympathetic crisis. A combination of hydrogenated ergot alkaloids are said to possess a highly sympatholytic action. The results with these drugs has had only transient effect, the intraocular pressure rising even during the continuance of these alkaloids. If glaucomas were due to sympathetic overactivity, the effects of these alkaloids should have been more marked and prolonged. These drugs instantaneously relieve pain irrespective of the severity and type of glaucoma. This has led to the conclusion that probably ocular pain is mediated through the sympathetic. Though blood pressure is also reduced by the administration of this drug, no correlation between the fall in blood pressure and intraocular pressure could be established. The value of this drug from the clinical and pharmacologic point of view is equivocal as far as the etiology of glaucoma is concerned. Due to similar results in simple and congestive glaucoma, it has been considered inadvisable to classify simple and congestive glaucoma as two separate etiologic entities. In conclusion it may be said that the drug is principally of value for preoperative treatment and relief of pain in glaucoma. 13 references. 6 tables.—*Author's abstract.*

LACRIMAL APPARATUS

65. *Congenital Alacrimia in Familial Autonomic Dysfunction.* JOHN H. DUNNINGTON. Presented at the 90th annual meeting of the American Ophthalmological Society, Glacier Park, June 16–18, 1954.

In the syndrome of familial autonomic dysfunction described by Riley et al, a congenital absence of tears is a constant finding. Skin blotching, drooling, emotional instability, motor incoordination, and relative indifference to pain are other diagnostic features. Since corneal ulceration is a frequent complication, a more detailed description of this disease entity was recorded.

EYELIDS

66. *Treatment of Chronic Lid Conditions.* ARTHUR A. SINISCAL, Rolla, Missouri. Eye, Ear, Nose & Throat Monthly. *33*:221–228, April 1954.

Chronic lid conditions commonly met with in practice are discussed, with a

presentation of differential diagnostic points and the modern method of treatment. Conditions discussed in detail include trachoma, inclusion blenorrhea, vernal catarrh, follicular conjunctivitis, blepharitis marginalis, trichiasis and districhiasis, symblepharon, ankyloblepharon and blepharophimosis, entropion, ectropion, lagophthalmos, Parinaud's conjunctivitis, and oculoglandular tularemia. Trachoma remains a disease of importance clinically because of its late sequelae and lid deformities resulting from many decades of slow cicatrization of the ocular membranes.

Indicated surgical procedures are listed, and some are discussed with further reference to collateral reading. The procedure for entropion surgery is illustrated with 8 figures, and the proper method of exposing the upper eyelid and fornices in the search for conjunctival disease is illustrated with 3 figures. 10 references. 9 figures.—*Author's abstract.*

MEDICAL OPHTHALMOLOGY

67. *Ophthalmoscopic Examination in Routine Office Practice.* ABRAHAM SCHLOSSMAN, New York, New York. Eye, Ear, Nose & Throat Monthly. *33*:178–179, March 1954.

The study and observation of the fundi afford the ophthalmologist a unique opportunity to draw conclusions as to the state of the general vascular and neurologic systems, as well as the metabolic and endocrine functions. The information obtained by careful ophthalmoscopic study may prove of value in several respects:

(1.) *Discovery of systemic disease.* The ophthalmologist may be the first physician to discover the presence of a general systemic disorder. This is especially true of diabetes, essential hypertension, brain tumor, and multiple sclerosis. The pinpoint aneurysms and hemorrhages, particularly in the macular area, may be present in very mild diabetics who have no symptoms of diabetes and are pathognomonic. A sudden increase in myopia in the presence of normal fundi should arouse a suspicion of diabetes.

(2.) *Discovery of an unsuspected pathologic process in a disease which has been diagnosed.* Certain less common diseases may cause fundus changes at some time during their course. As examples there may be cited the occurrence of miliary tubercles in the retina of a patient with a tuberculous focus elsewhere in the body, or the appearance of Roth's spots in the retina of a patient with subacute bacterial endocarditis. Both of these conditions signify a dissemination of the bacteria via the blood stream. Also, a metastasis of a tumor, especially from the breast, may be noticed in the retina before it is discovered elsewhere in the body.

(3.) *How the Ophthalmologist Can Help the Internist.* A patient with a chronic medical ailment may visit his ophthalmologist in order to have his refraction checked. In such a case, the internist frequently instructs the patient to have his ophthalmologist check the fundi carefully and to send him a report. In other cases, however, the ophthalmologist may actually corroborate the internist's diagnosis.

(4.) *Fundoscopic Examination in the Absence of Systemic Disease.* The ophthalmologist should have a complete record of the patient's fundus findings, especially of the disks, because at some time in the future the patient may develop a systemic disorder. At such time, a detailed description of the fundi may serve to clear up diagnostic points and to establish the rate of progress of the disease. Various congenital or developmental formations of the disks may simulate papilledema. The most common is pseudopapilledema in which all markings such as disk margins and cups are obliterated, but the blind spots are normal and there are no hemorrhages. Another condition that simulates papilledema is hyaline tissue (drusen) in the nervehead. In these cases the blind spots are always enlarged but there are never any hemorrhages.—*Author's abstract.*

68. *Visual Changes in Malignant Exophthalmos.* JOSEPH IGERSHEIMER, Boston, Massachusetts. Combined Meeting of Section on Ophthalmology with Association for Research in Ophthalmology, June 24, 1954.

The malignant exophthalmos is characterized by its progressive nature, periorbital and lid edema, a diminution of resiliency by palpating the eyeball, a limitation of ocular motility, and often also of lidlag. Ophthalmoplegia and the exposure of the cornea are well-known complications. Much less attention has been given to visual changes that can occur on one or on both eyes and which can be very alarming. In such a case the great visual reduction may be combined with a papilledema, while the papilledema caused by increased intraocular pressure usually goes without visual failure. There is another rare group of patients who have a very diminished visual acuity but have normal fundus. Igersheimer reports about several such cases in which it was possible to demonstrate a central or paracentral scotoma. Several facts point to the possibility that malignant exophthalmos as well as other kinds of severe exophthalmos under certain circumstances press upon the optic nerve near the optic foramen with the result of a central scotoma and later on of an optic atrophy. As far as treatment is concerned, the course of the ocular involvement can be self-limiting. Occasionally a decompression operation is indicated.—*Author's abstract.*

69. *Lipochondrodysplasia (Gargoylism).* FRANK W. NEWELL, Illinois AND AUNE KOISTINEN, Helsinki, Finland. Combined Meeting of Section on Ophthalmology with Association for Research in Ophthalmology, June 24, 1954.

Lipochondrodystrophy is a familial metabolic disease with storage of a macromolecular substance in many tissues and a defect in the maturation of cartilage. There may be dwarfing kyphosis, arthrogryposis, corneal clouding, mental deficiency, partial deafness, reduced vision, hepatosplenomegaly, and cardiac hypertrophy. The skull is usually enlarged and the nasal bridge depressed. There may be hypertelorism, common supraorbital ridges and prognathism. The skin is coarse, the lips thick, the ears enlarged and the tongue large and protruding. The hair is coarse and often grey in color. The eyes of 3 patients dying with the condition

were obtained for pathologic study. As has been noted previously the most marked changes were observed in the cornea. Bowman's membrane in many areas was split or displaced by large vacuolated cells. These cells were five or six layers thick in some areas, but entirely absent in others. They were most marked near the corneal scleral lumbus. Bowman's membrance did not appear destroyed by the cells nor was it missing entirely, but rather divided into thin lemellae which were so arranged however that the basal layer of the epithelium never rested directly upon the vacuolated cells. These cells caused considerable irregularity in height of the immediately adjacent basal cells. The total thickness of the epithelial layer was not affected however. Many of the vacuolated cells appeared empty and without nuclei. When stained with aniline blue and fuchsin others showed displaced nuclei in lightly pink staining cytoplasm.

Although these vacuoles are most prominent near the limbus, the opacity seen clinically is most marked centrally. From the clinical description of these patients and from those in the literature it seems probable that these vacuolated cells do not contribute to the clinical ocular picture. Additionally these cells appear to be an exception to the customary pathologic change elsewhere in the eye and body in not clearly being a storage phenomenon in cells normally present.

The corneal lamellae were diffusely, but regularly, separated, and most interlemellar spaces were optically empty. In some sections stained with aniline blue and orange fuchsin a slightly pinkish material was deposited. The corneal corpuscles were diffusely swollen and filled with a reddish staining material which in many cases obscured the nuclei. Other cells had nuclei which were displaced peripherally by the cytoplasm.

The corneal endothelium of the first patient was vacuolated with many cells optically empty. A few cells contained pinkish staining cytoplasm. The changes were most marked in the central cornea and the peripheral endothelium was normal. This change which has not been described previously may well be a postmortem artifact. However, the vacuolation was observed in only this eye and the changes are far more marked than usually occurs postmortem. Additionally, the patient died within the hospital and autopsy followed death far more quickly than in the second and third patients. The corneas were of normal thickness.

The sclera was definitely less compact than usual and separated into many lamellae, some of which were filled with reddish staining material with the aniline blue and orange fuchsin stain. A few of the cells, initially described by Wecler were noted as small compact deeply staining with poorly defined nuclei.

The ciliary epithelium was hyperplastic in all eyes especially that of the first patient. Again however it could not be definitely determined whether or not this was a postmortem change. A few of these cells were vacuolated but most contained a homogenous pinkish cytoplasm.

Particular attention was directed to the retina because of the regularity with which ganglion cells are involved in the brain. An occasional retinal ganglion cell was dilated, but in general this layer was not abnormal and would not in itself attract attention. However, cells of the inner nuclear layer definitely appeared to be abnormally enlarged with eccentric and peripheral displacement of the nuclei.

Other portions of the eye were normal. In the right eye of the second patient, a large cyst was present between the pigmented and nonpigmented epithelium of the ciliary body.

The pia arachnoid of the optic nerve was diffusely thickened and infiltrated with reddish staining material without, however, any of the minute cells present in the sclera being noted in this area. The changes in all structures were best demonstrated with blue fuchsin and aniline orange. The infiltrating substance did not stain with Best's carmine or with Hotchkiss' polysaccharide stain. The material was not lipid, at least as far as staining with Sudan IV was concerned.

The nature of the defect is not clear. Originally thought to be a type of lipid deposition, in recent years it has been considered a polysaccharide. There is a possibility that a lipid, such as a gangliocide, is deposited in nervous cells or a mucopolysaccharide is deposited elsewhere. It is highly desirable that eyes removed in future cases be sectioned before fixation and the tissues placed in basic lead acetate, alcohol, acetone, and formalin respectively. Tissues so fixed will retain the abnormal constituent and its identification will be possible. 55 references. 12 figures.—*Author's abstract.*

70. *Choroidal Carcinoma Metastatic from the Male Breast.* C. H. GREER, London, England. Brit. J. Ophth. *38*:312–315, May 1954.

A histologically confirmed spheroidal-celled carcinoma of the left breast was radically excised when the patient (a worker with ultramarine dye) was 41 years old. Eight years later an attack of episcleritis in the left eye led to the discovery of a single choroidal metastatic tumor below the disc and others in the left lung and in both femora. An autopsy performed 14 months later confirmed the presence of multiple spheroidal-celled secondaries. Details are also briefly presented of the age, sex, primary source, and histologic type of 40 previously unpublished cases of metastatic choroidal carcinoma from the archives of the Institute of Ophthalmology, London, (1935–53). By comparison, during the same period the archives record 236 cases of retinoblastoma and 1,274 cases of malignant choroidal melanomata. 4 references. 4 figures.—*Author's abstract.*

HYGIENE, PROPHYLAXIS, OCCUPATIONAL OPHTHALMOLOGY AND INJURIES

71. *Intra-Ocular Foreign Bodies, Report of 102 Cases.* KAZIMIERZ RUBINSTEIN, Sheffield, England. Brit. J. Ophth. *38*:369–377, June 1954.

This report deals with 102 consecutive cases of intraocular foreign bodies which were treated in the Royal Hospital, Sheffield in the years between 1944 and 1953 among 4,500 ophthalmic inpatients. Twenty six foreign bodies were extracted by anterior route, 57 by posterior route (Mellinger magnet); in 15 cases the attempt at extraction failed, and in 4 cases no attempt was made. The following features are analyzed: age, sex, occupation of the patients, actual work in which

engaged at the time of accident, time of the day, of shift and seasonal incidence, delay in hospital attendance, side involved, type of foreign body, route of entry, localization in the eye, route of extraction, and complications. These particulars are related to the final visual results and to the final economical results that is to the time spent by patients in the hospital, time off work and the loss of earning capacity after the accident. 6 references. 13 figures, 5 tables.—*Author's abstract.*

MISCELLANEOUS

72. *Accommodative Response to the Eye to Electrical Stimulation of the Ciliary Ganglion in Cats.* ELWIN MARG, JOHNIE L. REEVES, AND WALLACE E. WENDT. Am. J. Optom. and Arch. Am. Acad. Optom. *31*:127–136, March 1954.

An investigation was made of the maintained gradation of parasympathetic innervation of accommodation by electrically stimulating the ciliary ganglion in cats. Electrical stimulation was provided by condenser differentiation of the output of a square wave oscillator to provide biphasic waves. The refractive state of the eye which showed the accommodative response was measured from the partially iridectomized cat's eye in situ with an eye refractometer. The relationship between stimulus voltage applied to the electrodes at the ciliary ganglion and the refractive state of the eye in diopters was determined. Varying the frequency while maintaining constant voltage yielded a linear relationship. Nembutal anesthesia does not appear to affect the peripheral accommodative mechanism because similar results were obtained with decerebration in place of nembutal.

The lower frequency threshold, independent of voltage, is 4 cycles per second. The upper frequency threshold is dependent on voltage and was found at least up to 35 cycles per second. The sensitivity of the frequency gradation mechanism increases with increasing voltage from 0.02 diopters per cycle to 0.12 diopters per cycle for the voltages used. The amplitude of accommodation in young cats appears to be about two diopters. Within a certain central range of frequency and voltage, these two parameters may be substituted for each other to provide a given level of accommodative response.

The significance of these data in the classification of the ciliary muscle as multiunit muscle is discussed.

The term "neurodiopter" is proposed to express that unit of neural innervation which changes accommodation one diopter.

Extrapolation of the data indicates a physiological range of accommodation above the physical range as proposed by Hess.

The linearity of the frequency gradation mechanism of accommodative innervation is discussed in relation to the linearity of the ratio of accommodative convergence to accommodation (AC/A).

BOOK REVIEWS

Clinical Orthoptics. MARY EVERIST KRAMER, C. V. Mosby Co., Kansas City, Mo., 1954. Pp. 500. Price $12.50.

This is the revised edition of *Clinical Orthoptics*, which is primarily a manual for students in the orthoptic field; but it is also a valuable and helpful book for all actively engaged in the practice of ophthalmology or orthoptics.

Chapters 1 to 4 give adequate information in the anatomy, physiology and neurology of the eye and the extrinsic eye muscles. Chapter 5 provides a fundamental knowledge of optics which is essential for an understanding of the optical imperfections of the eye and for treatment, with prisms and lenses, of many of the difficulties arising from such optical imperfections. The purpose and aim of orthoptics is discussed in chapter 6, along with suggestions on the selection of patients for orthoptic training. Criteria for cure, causes of failure, technics in office administration, and rules to be observed in prescribing home exercises are also discussed.

Chapters 7 to 15 are concerned with the cause, care, and treatment of tropias and phorias. Particular attention is given to the importance of a careful refractive analysis, from the standpoint of the relative accommodation and reducing the accommodative stimulus during squint therapy, especially in the "no fusion" cases. Improved home technics are discussed and the various instruments used in orthoptic training are described. Valuable information on vertical deviations is contained in chapter 14.

The surgical correction of strabismus is discussed in chapter 16, and the final chapter pertains to reading disabilities caused by an ocular imbalance.

The value of this book as a text is greatly enhanced by references and questions at the close of each chapter, and by numerous illustrations which contribute to the understanding of the text.—*B. Evelyn Taylor, R.N.*

Ophthalmologic Diagnosis, F. H. HAESSLER, Baltimore, Williams & Wilkins, 1953. Pp. 380.

The author's declared purpose is to select from the ophthalmologic literature, data necessary for diagnosis and to present them so that they are useful in assisting to recognize the nature of eye diseases.

The book is divided into nine chapters. The first five chapters are concerned respectively with a General Survey of the Patient, the Disturbances of Functions, Manifestations of Abnormalities in the Adnexa, the Anterior Segment, and the Media and Fundus. These chapters are intended to serve as an example of diagnostic procedure based on an abbreviated list of manifestations. The remaining four chapters, in which further comment is elaborated, consist of a series of essays on the Functions, the Adnexa, the Anterior Segment, and the Posterior Segment.

The book contains much useful information and although there are no photographs or realistic drawings of actual conditions, it is profusely illustrated by helpful diagrams somewhat akin to those which an instructor might sketch on a blackboard—*Joshua Zuckerman, M.D.*

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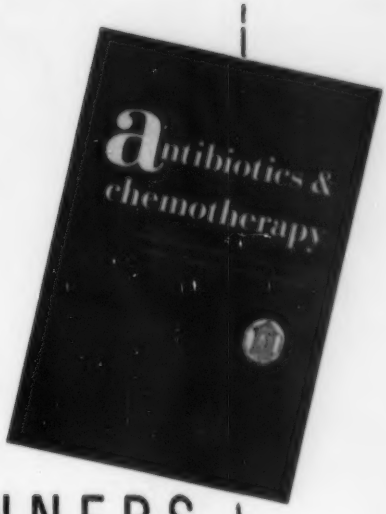

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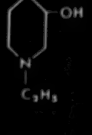
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